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Review article

Alterations in emotion generation and regulation neurocircuitry in depression and eating disorders: A comparative review of structural and functional neuroimaging studies

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ABSTRACT

Major depression and eating disorders (EDs) are highly co-morbid and may share liability. Impaired emotion regulation may represent a common etiological or maintaining mechanism. Research has demonstrated that depressed individuals and individuals with EDs exhibit impaired emotion regulation, with these impairments being associated with changes in brain structure and function. The goal of this review was to evaluate findings from neuroimaging studies of depression and EDs to determine whether there are overlapping alterations in the brain regions known to be involved in emotion regulation, evidence of which would aid in the diagnosis and treatment of these conditions. Our review of the literature suggests that depression and EDs exhibit common structural and functional alterations in brain regions involved in emotion regulation, including the amygdala, ventral striatum and nucleus accumbens, anterior cingulate cortex, insula, and dorsolateral prefrontal cortex. We present preliminary support for a shared etiological mechanism. Future studies should consider manipulating emotion regulation in a sample of individuals with depression and EDs to better characterize abnormalities in these brain circuits.

Contents

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1. Introduction

Epidemiological surveys have demonstrated that Major Depressive Disorder (MDD) and eating disorders (EDs) such as Anorexia Nervosa (AN), Bulimia Nervosa (BN), and Binge Eating Disorder (BED) frequently co-occur (Hudson et al., 2007). Individuals with a primary ED are 2–4 times more likely to develop MDD than individuals without an ED (Hudson et al., 2007). Similarly, a primary diagnosis of MDD is associated with increased risk for developing an ED, with 26% of adults with MDD reporting fasting to control weight and 19% reporting binge eating (Johnson et al., 2002). These data suggest that MDD and ED symptomatology do not occur in isolation and may therefore be important to investigate and treat simultaneously. Independently, MDD and EDs are serious illnesses with potentially devastating interpersonal and economic consequences, effects that are likely to be more pronounced when both disorders are present. Unfortunately, despite substantial efforts to develop effective treatments for both MDD and EDs, most available treatments do not produce demonstrable benefits for all patients (Brownley et al., 2007; Bulik et al., 2007; Holtzheimer and Mayberg, 2011; Shapiro et al., 2007). Understanding the mechanisms underlying the co-occurrence of MDD and EDs may lay the groundwork for the development of more targeted and efficacious treatments.

2. Role of emotion dysregulation in the pathology of depression and eating disorders

2.1. Defining emotion generation and regulation

Emotion generation and emotion regulation have been conceptualized in a variety of ways, and there is some debate as to whether these constructs are truly distinct from one another (Gross and Feldman Barrett, 2011). The perspective adopted in this review considers emotions to be discrete entities distinguishable from efforts to modify them, in accordance with the conceptualization offered by Gross (2015). As such, emotion generation is used herein to refer to the processes involved in the appraisal of a situation's meaning and its relevance to the pursuit of an active goal, and the subsequent generation of a corresponding emotion (e.g., feeling frustration when prevented from achieving a goal). Emotion regulation is used to refer to any process that is engaged for the purpose of modifying the experience or expression of an emotion. Emotion dysregulation arises when no attempt is made to modulate emotions, or the attempts are unsuccessful. This is particularly relevant in situations when failure to regulate emotions interferes with the pursuit of personally meaningful goals or significantly disrupts daily functioning. For a review of alternative models of emotion and emotion regulation, please see Gross and Feldman Barrett (2011).

2.2. Depression

Both MDD (Joormann and Gotlib, 2010) and EDs (Harrison et al., 2009; Naumann et al., 2015) are characterized in part by difficulties with emotion regulation, suggesting that emotion dysregulation may be one mechanism underlying their co-occurrence. Though emotion regulation only recently has garnered research attention in EDs, MDD has long been conceptualized as a disorder of dysregulated emotion (Beck et al., 1979; Beck, 2002; Campbell-Sills and Barlow, 2007; Joormann and Gotlib, 2010). Indeed, individuals with MDD exhibit enhanced responding to, and more thorough processing of, negative emotional stimuli (Bradley et al., 1995; Burke et al., 2005; Gotlib et al., 2004), as well as biases in attention (Gotlib et al., 2004) and memory formation (Bradley et al., 1995) that lead to preferential processing and storage of negative, mood congruent information. Moreover, individuals with MDD show greater physiological reactivity to stress (Burke et al., 2005) and are less effective at inhibiting negative emotions once they have been elicited (Joormann and Gotlib, 2010). Importantly, biased processing of, and increased responding to, negative information precedes the development of MDD (Joormann et al., 2007) and persists following recovery from a depressive episode (Joormann and Gotlib, 2007), indicating that emotion dysregulation increases risk for MDD.

Individuals with MDD are also more likely to utilize ineffective emotion regulation strategies relative to their healthy counterparts (Campbell-Sills et al., 2006; Kovacs et al., 2008). For example, depressed individuals reported greater use of emotion suppression to regulate their emotions and less use of more effective approaches like cognitive reappraisal (Campbell-Sills et al., 2006). The use of such maladaptive strategies has been associated with heightened intensity of emotions and increased depressive symptoms in cross-sectional (Campbell-Sills et al., 2006; Joormann and Gotlib, 2010) and prospective investigations (Silk et al., 2003). Children at high genetic risk for MDD exhibit impaired emotion regulation, with emotion dysregulation mediating the link between psychosocial stressors and symptoms of MDD (Kovacs et al., 2008). In addition, individuals with a history of MDD continue to rely on maladaptive emotion regulation strategies like suppression, even when explicitly instructed to apply more proactive strategies such as reappraisal of the meaning of an emotionally evocative situation (Ehring et al., 2010). Together, these findings indicate that emotion dysregulation is one mechanism by which MDD develops and is maintained.

2.3. Eating disorders

A growing body of research has documented abnormalities in emotion generation and regulation in ED populations. The affect regulation model of EDs proposes that disordered eating behaviors are used to decrease negative emotions (Stice, 2001). It

follows that disordered eating behaviors are temporally preceded by increases in negative affect or depressive symptomatology, a relationship that has been well documented. Individuals retrospectively report that periods of low mood often precede binge eating and/or purging (Arnow et al., 1992; Lynch et al., 2000). This finding is consistent with prospective data obtained using real-time ambulatory monitoring (Wonderlich et al., 2014a,b), longitudinal designs (Stice, 2001; Stice et al., 1998), and experimental manipulations of mood (Chua et al., 2004). Moreover, negative mood in combination with dietary restriction increases the risk for a subsequent binge eating episode (Cools et al., 1992; Stice, 2001). These findings provide some support for the hypothesis that disordered eating behaviors develop as a means of managing negative affect.

There is also evidence to suggest that individuals with EDs have difficulty accurately identifying emotions in themselves and others (Bydlowski et al., 2005; Speranza et al., 2007), which has been prospectively linked to the persistence and severity of ED symptoms (Markey and Vander Wal, 2007; Speranza et al., 2007). Emotion dysregulation is predictive of binge eating above and beyond other variables known to be prognostic of developing an ED such as dietary restriction (Whiteside et al., 2007). Further, emotion dysregulation is prospectively associated with maintenance and worsening of AN symptomatology (Racine and Wildes, 2015). Individuals with EDs tend to rely on maladaptive strategies such as emotion suppression and avoidance (Aldao et al., 2010; Haynos and Fruzzetti, 2011; Harrison et al., 2009; Whiteside et al., 2007), which amplify rather than diminish the intensity of negative emotions (Dalgleish et al., 2009; Haedt-Matt et al., 2014). Importantly, the relationship between ED symptomatology, ineffective emotion regulation, and negative mood has been observed in children who do not have a diagnosable ED but nevertheless experience a loss of control during eating (Czaja et al., 2009). This suggests that deficits in emotion regulation may be a developmental precursor to EDs (Sim and Zeman, 2006). Finally, psychotherapies that specifically target emotion dysregulation may be effective in the treatment of EDs (Chen et al., 2015; Johnston et al., 2015; Telch et al., 2001; Wilson et al., 2007; Wonderlich et al., 2014a,b). As such, there is evidence to suggest that emotion dysregulation may be involved in the onset and/or maintenance of ED symptomatology.

3. Overview of the neurocircuitry supporting emotion generation and regulation

Collectively, available data indicate that MDD and EDs are characterized by emotion dysregulation, which may explain the observed co-occurrence of these disorders. In healthy populations, structural and functional neuroimaging techniques have been used to elucidate the neural systems that give rise to emotion regulation (Ochsner et al., 2012). There is a large degree of overlap between regions that participate in emotion generation and those that participate in emotion regulation, and these regions may be differentially activated depending on the goals and demands of the situation (Ochsner et al., 2009; Ochsner et al., 2012). Evidence suggests that the amygdala, ventral striatum (VS), nucleus accumbens (NAc), anterior cingulate cortex (ACC), and insula are all involved in the appraisal of stimuli and the subsequent generation of context-appropriate emotional responses (Ochsner and Gross, 2014; Phillips et al., 2003). The prefrontal cortex (PFC) is essential for ongoing evaluation and selection of appropriate responses based on current goals, current emotional state, past experiences, and social norms (Phillips et al., 2003; Ochsner and Gross, 2014; Ochsner et al., 2012), and is thus integrally involved in both emotion generation and regulation. Medial PFC regions have been implicated in stimulus valuation and emotion generation (Etkin et al., 2011), and lateral PFC regions have been implicated in regulatory processes (Ochsner et al., 2009, 2012). The dorsolateral PFC (dlPFC) in particular is thought to contribute to processes requiring the integration of sensory signals, maintenance of attention on goal-relevant stimuli, and retrieval of pertinent memories for the purpose of planning and selecting appropriate, goal-relevant behavioral responses (Kaller et al., 2011; Philiastides et al., 2011). Emotion regulation is one form of these goal-directed, motivated processes, and successful modulation of emotional responses is partially dependent on dlPFC signaling (Ochsner et al., 2012). Together, these regions form a neural network that supports emotion generation and regulation, and altered signaling within this network has been implicated in problematic emotional responding and failures in emotion regulation (for a comprehensive review of this circuitry, refer to Ochsner et al., 2012 and Ochsner and Gross, 2014). Structural and functional alterations in the brain regions that support emotion generation and regulation might contribute to the pathophysiology of MDD and EDs.

A growing body of literature has documented alterations in the emotion generation and regulation neurocircuitry in MDD (Drevets et al., 2008) and EDs (Frank et al., 2007). However, because the MDD and ED literatures have largely remained separate, it is unclear whether MDD and EDs exhibit common alterations in the neurocircuitry supporting emotion regulation. Therefore, the goal of this review is to systematically describe what is known about structural and functional differences in the neurocircuitry implicated in emotion generation and regulation in both disorders, as well as areas of overlap and divergence. Understanding the neural mechanisms underlying the co-occurrence of MDD and EDs may improve our understanding of the biological pathways involved in the etiology or maintenance of both disorders, as well as reveal transdiagnostic endophenotypes, which may yield new insights for the diagnosis, treatment, and prevention of MDD and EDs.

Alterations in neural systems underlying emotion regulation have been characterized extensively in individuals with MDD, but less is known about the neurocircuitry subsuming emotion generation and regulation in EDs. As such, only meta-analyses or reviews of neuroimaging studies in MDD in the regions described above will be reviewed. Because there is more research examining the neural basis of emotion dysregulation in MDD relatives to EDs, findings in MDD will be used as a model for describing the more limited ED literature. Specifically, reviews of the primary literature in EDs will be limited to research examining the five regions most consistently identified in the MDD literature. An important consideration when evaluating neuroimaging studies in the ED literature is that the majority of these studies were primarily exploratory in nature and consequently included small samples and were not specifically designed to examine neural correlates of emotion regulation. In order to evaluate whether neuroimaging studies in the ED literature were sufficiently powered to detect a significant relationship between brain structure or function and diagnostic status, several previously reported effect sizes (Cohen's d) for each brain region were obtained from the MDD literature. Weighted mean effect sizes were calculated according to standard methods (Hedges and Olkin, 1985), and these values were used to compute the sample size required to achieve a similar effect at 80% power and $\alpha = 0.05$. It is important to note that the magnitude of effects observed in MDD may be different from those in EDs given that there are differences in etiology and clinical presentation across these disorders. However, the power analyses provided a basis to critically evaluate the limited ED literature. Effect sizes and computed sample sizes derived from the power analyses are listed in Table 1.

Table 1
Weighted mean effect sizes (Cohen's *d*) for structural and functional neuroimaging findings in the depression literature and total computed sample sizes needed to observe a similar effect in a comparison of two equally-sized groups at 80% power and $\alpha = 0.05$.

	Structural			Functional		
	Effect Size	Total *N*	Papers meeting *N* threshold (%)	Effect Size	Total *N*	Papers meeting *N* threshold (%)
Amygdala	0.17	545	0 (0)	0.76	56	4 (11)
VS/NAc	0.40	260	0 (0)	1.53	16	37 (97)
ACC	0.63	106	1 (8)	1.09	37	15 (39)
Insula	0.93	40	9 (69)	0.49	134	0 (0)
dlPFC	0.87	44	9 (69)	1.05	32	20 (53)

Note. Total *N* refers to the total sample size required to observe an effect of a given size. Conventional metrics for interpreting effects sizes are as follows: small effect = 0.20, medium effect = 0.50, large effect = 0.80. VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

4. Depression: alterations in emotion generation and regulation circuitry

4.1. Structural differences

Structural alterations have been identified across the brain in acutely depressed individuals relative to their healthy counterparts, many of which are located within the neural networks that participate in emotion generation and regulation (Drevets et al., 2008). Generally, meta-analytic reviews of studies examining regional structural differences in MDD found that currently depressed individuals exhibited reduced grey matter volume in the amygdala (Bora et al., 2012a,b; Hamilton et al., 2008; Sacher et al., 2012), VS/NAc (Bora et al., 2012a,b; Koolschijn et al., 2009), ACC (Bora et al., 2012a,b; Drevets et al., 2008; Du et al., 2012; Koolschijn et al., 2009; Lai, 2013; Sacher et al., 2012), and dlPFC (Bora et al., 2012a,b; Fu et al., 2013; Sacher et al., 2012). However, other meta-analytic investigations of structural variation in MDD failed to find significant differences in brain volume in the amygdala (Bora et al., 2012a,b; Fu et al., 2013; Kempton et al., 2011; Koolschijn et al., 2009) and none reported group differences in insula volume despite evidence from functional imaging studies highlighting the potential importance of this brain region in the appraisal of emotionally valenced information (e.g. Ochsner et al., 2012). Based on the available evidence, it appears that MDD may be related to volume reductions in regions implicated in emotion generation and regulation, but that this relationship may be modified by patient characteristics such as duration of illness, medication status, co-occurring psychiatric illness, and perhaps demographic characteristics. Future research should examine the role of such modifiers, and would benefit from the use of longitudinal methods to determine whether volume reductions increase risk for or are merely the consequence of being in a depressive episode.

4.2. Functional differences

The brain regions involved in emotion generation and regulation have been shown to exhibit functional differences in depressed individuals. These findings are summarized in Table 2. Altered signaling patterns have been most consistently identified in the amygdala, and have been documented across a broad range of functional imaging paradigms. The preponderance of relevant studies have observed heightened amygdala activation in response to sad, fearful, or angry faces among individuals with MDD (Delvecchio et al., 2012; Stuhrmann et al., 2011). Further, depressed individuals exhibit decreased amygdala reactivity to positively valenced expressions (e.g., happiness) relative to healthy individuals (Groenewold et al., 2013; Stuhrmann et al., 2011). Heightened responding to negative stimuli and dampened responding to positive stimuli is consistent with the cognitive literature in depression (e.g., Bradley et al., 1995; Burke et al., 2005; Gotlib et al., 2004; Yoon et al., 2009). Because antidepressant treatment is associated with reduced amygdala activation in response to negatively valenced stimuli (Delaveau et al., 2011), exaggerated amygdala reactivity to negative stimuli may be causally related to depression. This may reflect a relative disengagement of emotion regulation processes in favor of heightened emotional arousal driven by amygdala activity.

Striatal activation has similarly been associated with depression, with the direction of the effect being dependent on the valence of the stimuli used. In general, meta-analytic reviews have observed heightened putamen activity both at rest (Fitzgerald et al., 2008; however, see review published by Drevets et al., 2008), and in response to negative stimuli in depression (Diener et al., 2012; Fitzgerald et al., 2008; Groenewold et al., 2013; Stuhrmann et al., 2011). There is also evidence to suggest that striatal activation in response to positive affective stimuli is reduced in depressed individuals (Fitzgerald et al., 2008; Groenewold et al., 2013). Interestingly, elevated striatal activation at baseline has been shown to predict poor response to treatment (Fu et al., 2013) and antidepressant treatment produces significant reductions in striatal activation to negative stimuli (Fitzgerald et al., 2008). It should be noted that two meta-analyses found blunted striatal activation in depressed individuals in response to stimuli of positive (Delvecchio et al., 2012) and negative (Delvecchio et al., 2012; Hamilton et al., 2012) valence, findings that contradict those reported by the preponderance of identified meta-analyses. The meta-analysis conducted by Delvecchio et al. (2012) included fewer studies than others, some of which examined Bipolar Disorder rather than MDD, which likely explains the discrepant associations between striatal activation and depression. The meta-analysis conducted by Hamilton et al. (2012), in contrast, was largely similar to other meta-analyses identifying an effect of the striatum, and included many of the same primary articles. It is possible that the primary articles that did not overlap across meta-analyses may be driving the discrepant findings reported by Hamilton et al. (2012). Nevertheless, these data indicate that individuals in a depressive episode exhibit mood congruent biases in striatal processing of affective stimuli, which may underlie changes in behavioral responses to emotional arousal and diminished motivation.

Meta-analytic reviews have consistently identified signaling alterations in the ACC in response to a variety of stimuli among depressed individuals. In general, individuals with MDD exhibit heightened activation throughout the ACC compared to healthy individuals. Meta-analytic reviews of task-evoked regional activation in MDD have documented elevated ACC activation in response to negatively valenced stimuli (Delvecchio et al., 2012; Groenewold et al., 2013; Hamilton et al., 2012; Stuhrmann et al., 2011), and blunted activation in response to positive stimuli (Groenewold et al., 2013; Stuhrmann et al., 2011) and during cognitive tasks (e.g. memory encoding, error processing; Diener et al., 2012). Higher ACC activation during a depressive episode has been shown to predict a more robust response to treatment (Fu et al., 2013), and ACC activation in response to negatively valenced stimuli has been shown to decrease with antidepressant treatment (Delaveau et al.,

Table 2
Summary of functional neuroimaging findings among individuals with Major Depressive Disorder during illness and recovery.

	MDD		Rec-MDD	
	Negative stimuli	Positive stimuli	Negative stimuli	Positive stimuli
Amygdala	↑	↓	↓	–
VS/NAc	↑↓	↓	↓	–
ACC	↑	↓	↓	–
Insula	↑↓	–	↓	–
dlPFC	↑↓	–	↑	–

Note. All findings are derived from comparisons with healthy individuals. Findings in individuals recovered from depression were obtained from treatment studies. Dashes indicate that there were no studies reporting pertinent findings. MDD = Major Depressive Disorder; Rec = recovered; VS = ventral striatum; NAc = nucleus accumbens; ACC = Anterior Cingulate Cortex; dlPFC = dorsolateral prefrontal cortex.

2011), providing some evidence that ACC activity is involved in the pathophysiology of MDD.

Functional alterations in the insula have also been identified among depressed individuals. Several meta-analytic reviews have demonstrated that individuals with depression exhibit decreased activity in the insula when processing negatively valenced stimuli or following the induction of a negative mood state (Diener et al., 2012; Fitzgerald et al., 2008; Stuhrmann et al., 2011). However, a meta-analysis of comparable size conducted by Hamilton et al. (2012) revealed the opposite effect of insula activation among depressed individuals. This latter finding is more consistent with investigations of the effect of treatment on insula activity, which have demonstrated that higher insula activation at baseline predicts poor response to antidepressant treatment (Fu et al., 2013), and treatment is associated with decreased insula activity (Delaveau et al., 2011). Research examining interoceptive awareness among depressed individuals has produced equivocal results, with some studies observing reduced awareness (Dunn et al., 2010; Pollatos et al., 2009), and others finding no difference (Dunn et al., 2007). These discrepancies in behavioral studies may be related to the inconsistencies in the neuroimaging literature regarding the nature of the relationship between insula activation and MDD. It is possible that there are subgroups of individuals with depression for whom interoceptive awareness and insula activation factor strongly in their symptom presentation, while these processes may be less relevant for others. Nevertheless, all of the identified meta-analyses but two (Delvecchio et al., 2012; Sacher et al., 2012) documented changes in insula signaling among depressed individuals, indicating that this region may contribute to emotional impairments in MDD.

Signaling alterations in the dlPFC among individuals with MDD have been observed, though there is disagreement as to whether MDD is characterized by dlPFC hyperactivation or hypoactivation (Fitzgerald et al., 2006). The majority of reviews have found blunted responding to negative affective stimuli among depressed individuals compared to healthy controls (Diener et al., 2012; Fitzgerald et al., 2008; Groenewold et al., 2013; Hamilton et al., 2012). Further, dlPFC activation during an affective switching task, which requires patients to flexibly respond to abrupt changes in positive and negative reinforcement contingencies, is reduced among depressed patients (Diener et al., 2012). This suggests that dlPFC signaling may underlie deficits in emotional and reward-based learning evident in MDD. However, the meta-analysis conducted by Diener et al. (2012) also found that depressed individuals exhibited greater dlPFC activation following a negative mood induction and during working memory tasks. It is possible that individuals with MDD fail to adequately recruit the dlPFC when engaged in tasks involving relatively minimal cognitive processing (e.g., appraisal of stimuli with obvious affective valence), yet more strongly engage the dlPFC to adequately perform on cognitively demanding tasks (e.g., recall of a sad memory, retaining information in working memory for later use), the latter perhaps reflecting a compensatory response to diminished cognitive capacity associated with MDD. Finally, two meta-analyses have revealed that dlPFC activation increases following a successful course of antidepressant treatment (Delaveau et al., 2011; Fitzgerald et al., 2008). Further, repeated transcranial magnetic stimulation applied directly to the dlPFC leads to remittance of depressive symptoms (Schutter, 2009). Together, these studies provide evidence that changes in dlPFC signaling may be one mechanism through which MDD develops, and may be an important target for treatment.

5. Eating disorders: alterations in emotion generation and regulation circuitry

5.1. Structural differences

Relative to the literature examining differences in brain structure in MDD, there have been far fewer studies examining the neural correlates of EDs, particularly BN and BED. The available evidence suggests that individuals with BN exhibit reduced caudate and putamen volume compared to healthy individuals (Amianto et al., 2013; Coutinho et al., 2015; Frank et al., 2013a) and individuals with AN (Amianto et al., 2013). There also is evidence that individuals with BN show increased VS volume compared to healthy individuals and individuals with BED (Schäfer et al., 2010). One study observed higher insula volume among acutely ill individuals with BN compared to healthy individuals (Frank et al., 2013a), a pattern that may persist in recovery from BN (Wagner et al., 2006). Individuals with BED have been shown to have higher ACC volume relative to healthy individuals, but ACC volumes did not differentiate individuals with BED from those with BN (Schäfer et al., 2010), perhaps due to the overlap in symptoms of BN and BED. Evidence of other specific regional volumetric alterations in BN or BED is currently lacking, though the absence of findings is likely attributable to the fact that few studies have sought to characterize these alterations in BN and BED. This represents an important area for future research.

Regional structural alterations have been documented more frequently in AN than BN and BED. In general, AN is characterized by volume reductions across the brain, and specifically in the regions highlighted below. The two most consistently observed regional volume reductions among individuals with AN are in the amygdala (Friederich et al., 2012; King et al., 2015) and the ACC (Boghi et al., 2011; Friederich et al., 2012; Joos et al., 2010; King et al., 2015; McCormick et al., 2008; Mühlau et al., 2007). Interestingly, amygdala (Friederich et al., 2012; King et al., 2015) and ACC volumes have been shown to normalize with treatment (King et al., 2015), suggesting that reduced amygdala and ACC volume may be state markers of AN that are sensitive to weight restoration. Indeed, a prospective investigation of the relationship between weight restoration and ACC volume demonstrated that inpatient treatment was associated with normalized ACC volume (McCormick et al., 2008). However, the majority of studies reporting a relationship

Table 3
Number of functional imaging studies reporting positive findings among individuals with eating disorders.

	Food paradigms	Body image paradigms	Affective paradigms	Reward paradigms
Amygdala	3	4	2[a]	1
VS/NAc	6[a]	2	1	5
ACC	7[b]	2	1[a]	3
Insula	12[a]	5	0	3
dlPFC	4	3[a]	2[a]	0[a]
Total studies	16	12	9	5

Note. There were a total of 42 papers reporting findings obtained from 38 different samples due to the fact that several papers used a sample previously described in another publication. VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

[a] One study specifically examined responses in this region but did not observe significant differences in activation.

[b] Two studies specifically examined responses in this region but did not observe significant differences in activation.

between amygdala and/or ACC volume and acute AN were cross-sectional, making it difficult to confirm that differences between acute AN and weight restored AN groups are attributable only to the effects of treatment. Further, several studies, including a small meta-analysis, examining regional grey matter differences in AN did not find evidence that ACC volumes differentiate individuals with AN from healthy individuals (Brooks et al., 2011a,b; Frank et al., 2013a; Gaudio et al., 2011; Titova et al., 2013). According to the power analyses reported in Table 1, few of the studies examining structural variation among individuals with an ED were statistically powered to detect an effect in either the amygdala or ACC, which likely explains some inconsistencies in the literature. With these considerations in mind, the available evidence indicates that amygdala and ACC volumes are reduced in symptomatic individuals with AN and normalize with treatment, though additional research is necessary to confirm these preliminary observations.

Structural alterations in the striatum and NAc, the insula, and dlPFC have also been noted among individuals with AN, but the direction of these relationships is inconsistent across studies. For instance, several studies have demonstrated that individuals with acute AN exhibit reduced caudate (Boghi et al., 2011; Titova et al., 2013), putamen (Friederich et al., 2012), and NAc (King et al., 2015) volumes relative to healthy individuals, though others have reported no group differences (Frank et al., 2013a) or increased volume (Frank et al., 2013b) in these regions. Similarly, insula volume has been shown to be lower among acutely ill individuals with AN in one study (Brooks et al., 2011a,b), but elevated in others (Frank et al., 2013a,b). It is important to note that the studies that have observed higher rather than lower regional volumes among individuals with AN were conducted by the same group (Frank et al., 2013a,b). The authors suggest that their discrepant findings may be attributable to the implementation of a more advanced approach to segmenting brain structures in a comparatively large sample (acute AN sample size = 19 compared to 14 in Brooks et al., 2011a,b). Although there are some data to suggest that the segmentation method used by Frank et al. (2013a,b) may be more accurate than other methods (Eggert et al., 2012), it is not clear whether the differences in their findings are meaningful or reliable without replication. Finally, the two studies reporting differences in dlPFC volume among individuals with AN observed opposite effects (Boghi et al., 2011; Brooks et al., 2011a,b), though neither study was adequately powered to detect an effect in this region. Overall, it is difficult to determine whether these discrepancies in the direction of the effect of NAc, insula, and dlPFC volume are meaningful, emphasizing the need for further research conducted in larger samples.

5.2. Functional differences

A variety of paradigms have been used to assess task-evoked differences in regional brain activity in ED populations. The clinical and etiological implications of functional neuroimaging findings are dependent upon the task used to evoke neural responses. Further, few studies have used tasks that specifically target emotional arousal or regulation, representing a major limitation of the available evidence. Thus, regional differences in activation described in the following sections will be distinguished by neuroimaging paradigm. Table 3 summarizes the number of studies that used each paradigm and the proportion of those studies reporting positive findings.

5.2.1. Amygdala

5.2.1.1. Food paradigms. There are a few studies that have identified a link between amygdala activity and the processing of food cues, though the evidence for this relationship is limited. For instance, individuals with AN have been shown to exhibit elevated amygdala reactivity to food images (Joos et al., 2011a,b,c) and when ingesting a chocolate milkshake after fasting compared to healthy individuals (Vocks et al., 2011), even after controlling for symptoms of MDD (Joos et al., 2011a,b,c). These findings indicate that individuals with AN regard food as aversive, particularly when hungry, which may reflect a fear of weight gain or loss of control of eating triggered by food. Among individuals with BN and subthreshold BN, negative affect has been associated with greater functional connectivity between the amygdala, caudate, and insula while anticipating the receipt of a milkshake (Bohon and Stice, 2012). One interpretation of this finding is that increased amygdala activation during a negative affective state may enhance the reward value of palatable food via its connections to midbrain regions like the caudate known to be involved in the evaluation of rewards (Bohon and Stice, 2012). Together, these three studies provide initial evidence that amygdala responses to visual or gustatory food stimuli are elevated among individuals with EDs, which may constitute a neurobiological link between negative affect and aberrant eating (Table 4). Nevertheless, while the positive findings linking amygdala responses to food cues with AN are intriguing, additional research is necessary to evaluate the strength and replicability of this relationship.

5.2.1.2. Body image paradigms. Several studies have demonstrated that individuals with AN exhibit relatively higher amygdala activation when viewing stimuli related to body composition. For instance, amygdala activation in response to pictures of their own bodies (Seeger et al., 2002) and other women's bodies (Pruis et al., 2012; Vocks et al., 2010) was shown to be elevated among women with AN, but not among those with BN (Vocks et al., 2010) or healthy individuals (Seeger et al., 2002; Vocks et al., 2010). A similar pattern was observed when participants were presented with words associated with negative body image (e.g., heavy; Miyake et al., 2010a). Women with BN exhibited significantly less amygdala activation in response to negative body image stimuli than did individuals with AN (Miyake et al., 2010a,b) or healthy individuals (Miyake et al., 2010b), despite evidence that individuals with BN are more dissatisfied with their bodies than are individuals with AN (Cash and

Table 4
Summary of regional activation patterns in response to food paradigms among individuals with eating disorders.

	AN	Rec AN	BN	Rec BN	BED	Rec BED
Amygdala	↑	–	↑	–	–	–
VS/NAc	↑ ↓	↑ ↓	↑	–	BED > BN, HC, OW	–
ACC	AN > BN, HC	↑ ↓	↑ ↓BN > BED	↓	BED < BN	–
Insula	↑ ↓	↑ ↓	↑ ↓BN > BED	↑	↑	–
dlPFC	↓	↑,Rec AN > AN	↓	–	–	–

Note. Comparisons are with healthy individuals except where noted. Arrows indicated the direction of reported effects. Larger arrows indicate stronger evidence that the effect is in the direction of the arrow. Dashes indicate that there were no studies reporting pertinent findings. AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; Rec = recovered; HC = healthy control; OW = overweight; VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

Table 5
Summary of regional activation patterns in response to body image paradigms among individuals with eating disorders.

	AN	Rec AN	BN	Rec BN	BED	Rec BED
Amygdala	AN > BN, HC	–	BN < AN, HC	–	–	–
VS/NAc	↑	–	–	–	–	–
ACC	↓	–	↑	–	–	–
Insula	↓ ↑	–	↑	–	–	–
dlPFC	↓ ↑	–	↓	–	–	–

Note. Comparisons are with healthy individuals except where noted. Arrows indicated the direction of reported effects. Larger arrows indicate stronger evidence that the effect is in the direction of the arrow. Dashes indicate that there were no studies reporting pertinent findings. AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; Rec = recovered; HC = healthy control; VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

Table 6
Summary of regional activation patterns in response to emotion paradigms among individuals with eating disorders.

	AN	Rec AN	BN	Rec BN	BED	Rec BED
Amygdala	x	x	↓	–	–	–
VS/NAc	x	x	↓	–	–	–
ACC	↓	↓	↓	–	–	–
Insula	x	x	x	x	–	–
dlPFC	↑	x	↓	–	–	–

Note. All comparisons are with healthy individuals. Arrows indicated the direction of reported effects. An x indicates that one or more studies reported no differences between groups. Dashes indicate that there were no studies reporting pertinent findings. AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; Rec = recovered; HC = healthy control; VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

Deagle, 1997). However, further research in larger samples will be necessary to provide more convincing evidence of the amygdala's role in emotion-driven appraisal of body image cues in EDs (Table 5).

5.2.1.3. Emotion paradigms. Among the few studies examining neural correlates of emotion generation among individuals with EDs, several have documented alterations in amygdala activity. For example, individuals with BN have been shown to exhibit reduced amygdala activation to emotionally salient stimuli like negative personality words (e.g., monstrous; Pringle et al., 2011) and angry or disgusted facial images (Ashworth et al., 2011) compared to healthy individuals. However, another study did not observe any significant differences in regional brain activation to disgust or fear-related words among individuals with BN (Schienle et al., 2004). Among individuals with AN, heightened amygdala activation during the processing of fear-related words was negatively associated with alexithymia scores (Miyake et al., 2012). Interestingly, no differences in neural responses to emotional facial expressions were evident when comparing healthy individuals to individuals with AN in sustained recovery (Cowdrey et al., 2012), indicating that neural and behavioral abnormalities in emotion generation are improved with treatment. Notably, only the study conducted by Cowdrey et al. (2012) designated the amygdala as an a priori ROI. As such, the absence of significant findings in other studies may reflect the fact that they were underpowered to detect an effect in the amygdala and did not set out to do so using more relaxed thresholds in an ROI analysis (Table 6).

5.2.1.4. Reward paradigms. Functional variation in amygdala activation during reward processing tasks has not commonly been observed in individuals with EDs. Of the five studies examining reward processing in EDs, only one documented differences in amygdala activation. Specifically, individuals with BN were shown to exhibit reduced amygdala activation during the unexpected receipt of a reward or omission of an expected reward, with higher amygdala activation predicting less frequent binge/purge episodes (Frank et al., 2011). This may suggest that amygdala response to altered reward contingencies is an index of disorder severity. However, because only one study examining neural correlates of reward processing in EDs has tested the effect of the amygdala in an ROI analysis, further research is necessary to better characterize the role of the amygdala in reward valuation and reward learning among individuals with EDs (Table 7).

5.2.2. Ventral striatum/nucleus accumbens

5.2.2.1. Food paradigms. Several studies have demonstrated that individuals with EDs exhibit altered VS/NAc signaling patterns in response to food, particularly among those who binge eat. For example, individuals with BN exhibited greater activation in the caudate in response to palatable food images (Brooks et al., 2011a,b) and when anticipating receipt of a milkshake (Bohon and Stice, 2012) compared to individuals with AN (Brooks et al., 2011a,b) and healthy individuals (Bohon and Stice, 2012). Striatal activity was positively associated with self-reported negative affect, indicating that individuals with BN may be particularly responsive to food reward during periods of low mood (Bohon and Stice, 2012). Increased VS activation has also been shown to differentiate individuals with BED from overweight individuals without BED (Weygandt et al., 2012), providing evidence that VS responses to food are specifically related to binge eating behavior. While no studies have reported differences in VS/NAc activation among individuals with acute AN, two studies have documented differences in VS/NAc signaling among individuals who have recovered from AN. Specifically, one study observed elevated VS activation in response to the taste of palatable food and elevated striatal activation in response to aversive tastes among recovered individuals relative to their healthy counterparts (Cowdrey et al., 2011). In contrast, Wagner et al. (2008) observed reduced striatal activation in response to sweet tastes among individuals recovered from AN compared to healthy individuals. Both studies included only individuals recovered from restricting-type AN, used similar definitions of recovery, and had similar sample sizes, suggesting that the source of the discrepancy may be related to imaging parameters (e.g., magnet strength, task design), or reflect instances of type I error. The

Table 7
Summary of regional activation patterns in response to reward paradigms among individuals with eating disorders.

	AN	Rec AN	BN	Rec BN	BED	Rec BED
Amygdala	x	x	↓	x	x	–
VS/NAc	↑ losses↓ valuation	↓	↓	↓	↑ anticipation↓ receipt	–
ACC	↑ losses↓ valuation	↑ ↓	x	x	↓	–
Insula	x	↓	↓	x	↓	–
dlPFC	↓	–	x	x	x	–

Note. All comparisons are with healthy individuals. Arrows indicated the direction of reported effects. An x indicates that one or more studies reported no differences between groups. Dashes indicate that there were no studies reporting pertinent findings. AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; Rec = recovered; HC = healthy control; OW = overweight; VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

latter hypothesis is supported by Oberndorfer et al. (2013a), who failed to find a relationship between NAc/VS activation and diagnostic status among individuals in recovery from AN and BN in ROI analyses conducted to test a priori hypotheses about these regions. This raises the possibility that VS/NAc signaling variation does not contribute to EDs, particularly AN (Table 4).

5.2.2.2. Body image paradigms. There is some evidence that variation in striatal activity differentiates individuals with EDs from their healthy counterparts. Specifically, using an ROI approach to isolate responses in the VS, individuals with AN were found to exhibit elevated VS activation in response to images of underweight women relative to images of normal weight women, a pattern that was not evident among healthy individuals (Fladung et al., 2010). Similar results were obtained by Friederich et al. (2010) in whole-brain exploratory analyses of neural responses to images of thin models. These findings may be interpreted as evidence that individuals with AN derive pleasure from looking at people who are underweight, which may translate into pleasurable feelings in response to their own weight loss and underlie the pursuit of thinness in AN. It should be noted that the majority of studies did not detect an effect in the VS/NAc, leaving open the possibility that the positive findings described herein are spurious (Table 5).

5.2.2.3. Emotion paradigms. There is limited evidence that individuals with an ED exhibit altered VS/NAc responses during the processing of emotional stimuli. One study observed blunted striatal activity in individuals with BN compared to healthy individuals when evaluating negative personality traits (Pringle et al., 2011). Reduced responsivity to negative self-referent words may reflect that individuals with BN possess negative self-schema and thus exhibit less arousal when presented with words that are consistent with their negative beliefs about themselves. Alternatively, reduced limbic responses to negative self-referent words may be indicative of emotional blunting (Pringle et al., 2011; Table 6). These interpretations should be considered preliminary and in need of further testing, particularly given that eight other studies did not observe an effect in the striatum.

5.2.2.4. Reward paradigms. As expected, alterations in VS/NAc signaling during reward processing tasks have been identified in all of the included studies of individuals with EDs. For example, adolescents with AN have been shown to exhibit elevated caudate responses to monetary losses compared to healthy adolescents, which may underlie perfectionism often observed among individuals with AN (Bischoff-Grethe et al., 2013). One study demonstrated that healthy individuals exhibit heighted VS responsivity during a reward related decision making task when hungry, but greater activation in cognitive control regions when satiated, a pattern that was absent among individuals recovered from AN (Wierenga et al., 2015). This finding may be interpreted as evidence that reward drive and motivation are not modulated by metabolic state among individuals with AN, a deficit that persists in recovery and may be causally related to AN pathology. Individuals with BN have been shown to exhibit reduced striatal responses when they do not receive a reward that they expect based on previous learning (Frank et al., 2011), with this effect persisting in recovery (Wagner et al., 2010). Similarly, VS activity during the anticipation of monetary reward and loss was found to be lower among individuals with BED compared to obese individuals without BED (Balodis et al., 2013). Together, these findings suggest that individuals with an ED, particularly BN and BED, fail to update contingencies based on new information about the relationship between behavior and receipt of reward, which is reflected in abnormal striatal activation during reward tasks (Table 7).

5.2.3. Anterior cingulate cortex

5.2.3.1. Food paradigms. Altered activation patterns in the ACC in response to food stimuli have been shown to differentiate individuals with EDs from healthy individuals in some studies. For instance, women with AN and BN exhibited elevated ACC activation in response to food images (Uher et al., 2004). Increased ACC activation has also been observed during the ingestion of both pleasant and aversive food among individuals with AN, but not among healthy individuals (Cowdrey et al., 2011). A recent meta-analysis observed a consistent pattern of increased ACC activation among individuals with AN relative to their healthy counterparts (Zhu et al., 2012). Individuals in sustained recovery from AN exhibited higher ACC activation in response to food cues compared to both healthy controls and acutely ill individuals with AN (Uher et al., 2003). However, studies specifically examining ACC responses to high calorie food using an ROI approach failed to identify significant differences in ACC activation among acutely ill individuals with AN (Joos et al., 2011a,b,c) or individuals in sustained recovery from AN or BN (Oberndorfer et al., 2013a; Table 4). Thus, although there is some preliminary evidence that ACC activation in response to food is elevated in AN and may even be more pronounced during sustained recovery, additional research is necessary to confirm this relationship.

Individuals with BN have also been found to exhibit elevated ACC activity in response to food cues relative to individuals with BED and overweight and normal weight individuals without an ED (Schienle et al., 2009). It should be noted that the opposite pattern of ACC activation was observed in a slightly smaller sample ($n = 10$ compared to $n = 14$; Joos et al., 2011a,b,c). During recovery, individuals with BN exhibited lower ACC activation in response to glucose intake when compared to healthy individuals (Frank et al., 2006). Therefore, in contrast to AN, BN may be characterized by elevated ACC activation during acute illness that normalizes with recovery, a question in need of further exploration given discrepancies in the available literature (Table 4).

5.2.3.2. Body image paradigms. Two studies to date have observed differential patterns of ACC activation in response to body image cues among individuals with an ED. Specifically, when comparing their own body to the slim bodies of models, individuals with AN exhibited reduced ACC activation relative to healthy individuals, with lower ACC activation being associated with lower

self-reported anxiety (Friederich et al., 2010). Reduced ACC activation to images of thin women among those with AN may reflect reduced emotional arousal and conflict about being thin. ACC activation has been shown to be greater among women with BN relative to healthy individuals when viewing images of overweight women (Spangler and Allen, 2012), perhaps reflecting the activation of thoughts about the discrepancy between the desire to be thin and actual or perceived body weight among women with BN (Table 5). One consideration in interpreting these findings is that the majority ($n = 10$) of studies exploring the relationship between neural responses to body images and ED did not detect an effect in the ACC. On the other hand, none of the studies examining this question designated the ACC as an a priori ROI to be specifically tested in statistical analyses, leaving open the possibility that there was an effect of the ACC that went undetected in whole-brain analyses.

5.2.3.3. Emotion paradigms. Only one study observed significant differences in ACC activity among individuals with an ED during the presentation of emotionally salient stimuli. Specifically, when asked to reflect on personal attributes and how others perceive them, individuals with a history of an ED exhibited lower activation in the ACC compared to healthy individuals in an ROI analysis (McAdams and Krawczyk, 2013). It is possible that decreased ACC activation during self-reflection may be related to over-reliance on strategies like avoidance to regulate negative emotions, and may underlie interpersonal difficulties experienced by individuals with EDs (Table 6). In contrast to this finding, Pringle et al. (2011) did not observe an expected relationship between BN and ACC activation during the evaluation of negative personality traits. It is possible that this apparent discrepancy is explained by the fact that McAdams and Krawczyk (2013) examined ACC responses to emotional stimuli in recovered individuals, whereas Pringle et al. (2011) examined this relationship in acutely ill individuals, which is suggestive of a state-dependent difference in the processing of emotional stimuli in the ACC. However, additional research is necessary to rule out the possibility that one or both of these findings is spurious, particularly given that other studies did not observe an effect in the ACC.

5.2.3.4. Reward paradigms. Three of five studies examining the neural correlates of reward processing among individuals with EDs using whole-brain analyses have observed alterations in ACC activation. For instance, adolescents with AN have been shown to exhibit exaggerated ACC responses to monetary loss compared to healthy individuals, which may be related to heightened sensitivity to mistakes and perfectionism characteristic of individuals with AN (Bischoff-Grethe et al., 2013). Individuals with a history of AN exhibited lower ACC activity when selecting immediately available over delayed rewards during a state of hunger compared to never-ill individuals, but higher ACC activity when satiated (Wierenga et al., 2015). This finding suggests that ACC activation during reward valuation is sensitive to metabolic state among healthy individuals, but not among individuals with a history of AN. This may explain why individuals with AN are able to deprive themselves of food even when starving, and suggests that insensitivity to metabolic state during reward valuation may be a trait marker of AN. Among individuals with BED, ACC activation during the anticipation and outcome phases of a monetary gambling task was found to be lower compared to normal and overweight individuals without an ED (Balodis et al., 2013). Failure to adequately recruit the ACC during a gambling task may reflect impairments in stimulus and outcome valuation among individuals with BED, which may contribute to binge eating (Table 7).

5.2.4. Insula

5.2.4.1. Food paradigms. Alterations in anterior insula activation in response to food stimuli have been documented among individuals with EDs in 11 of the 16 studies to examine this relationship. For example, insula activation was found to be lower among women with AN compared to healthy women when satiated, while no differences were noted when hungry (Vocks et al., 2011). In contrast, another study found that individuals with AN and BN exhibited elevated insula activation and greater connectivity with areas of PFC in response to food when hungry (Kim et al., 2012). Insula activation during the anticipation of eating food was shown to be higher among weight restored individuals with AN (Oberndorfer et al., 2013b), but lower during actual tasting (Oberndorfer et al., 2013b; Wagner et al., 2008) compared to healthy individuals. Insula activation during anticipation of food correlated with self-reported pleasantness of the food among healthy individuals but not individuals with AN (Oberndorfer et al., 2013a), suggesting that there is a disconnect between valuation of and response to food among individuals with AN. Findings among symptomatic individuals with BN have been mixed, with three studies reporting elevated insula activation (Kim et al., 2012; Schienle et al., 2009; Weygandt et al., 2012), and two reporting reduced insula activation (Brooks et al., 2011a,b; Bohon and Stice, 2011) in response to food cues. It should be noted that Brooks et al. (2011a,b) only included 8 individuals with BN, compared to 14–20 in the other studies, and Bohon and Stice's (2011) sample was largely comprised of individuals with subthreshold BN. In contrast to women recovered from AN, women recovered from BN exhibit elevated insula responses to sweet taste, which may reflect heightened valuation of food and interoceptive awareness that could promote eating (Oberndorfer et al., 2013a). Overall, there is strong evidence that EDs are characterized in part by altered insula activation in response to food stimuli (Table 4).

5.2.4.2. Body image paradigms. There is some evidence that insula activation in response to body image cues is altered among individuals with EDs. Women with AN have been shown to exhibit higher insula activity than healthy women when viewing images of thin women (Friederich et al., 2012; Mohr et al., 2010), and during the appraisal of thin words relative to neutral words (Redgrave et al., 2008). These findings have been supported by a recent meta-analysis observing a similar pattern of insula activation in response to body image cues (Zhu et al., 2012). In contrast, individuals with AN were found to have lower insula activation than healthy individuals when viewing images of their own body than when viewing images of other bodies matched for BMI (Sachdev et al., 2008), which may reflect cognitive and/or emotional avoidance that could underlie body dissatisfaction and body image distortions typically seen in AN. Individuals with BN have been shown to exhibit similar insula activation patterns in response to images of slim women as those with AN (Van den Eynde et al., 2013; Table 5). Nevertheless, seven of 12 studies did not observe a significant effect in the insula. This leaves open the possibility that inconsistent findings may be attributable to variation in patient characteristics (e.g., comorbid diagnoses) or study methodology (e.g., magnet strength, recruitment procedures), which may exert particularly strong influence on results if the effect of the insula is small.

5.2.4.3. Emotion paradigms. No studies have documented differences in insula activation, suggesting that the insula does not participate in the evaluation of and response to emotional stimuli among individuals with an ED. However, none of the five studies to examine neural responses to emotion stimuli in ED populations were adequately powered to detect an effect in the insula. Therefore, it is premature to conclude that the insula is not involved in emotion generation among individuals with an ED.

5.2.4.4. Reward paradigms. Insula activation during the evaluation of rewards has been shown to differentiate individuals with an ED from healthy individuals in three of the five studies to examine this question. For example, healthy individuals were found to recruit the insula during a reward-based decision making task when satiated compared to hungry, a pattern that was not observed among individuals with AN (Wierenga et al., 2015). Individuals with BN have been shown to exhibit reduced insula activation upon the receipt of an unexpected reward or during the loss of an expected reward (Frank et al., 2011). These findings suggest that individuals with an ED fail to integrate interoceptive cues into their decision making, which may influence decisions about food and eating (Table 7). The two studies that did not identify an effect in the insula each only had 10 participants in their patient groups, much less than the studies with positive findings, though none of the studies examining this question were sufficiently powered to observe an effect in the insula. Consequently, it is possible that the effect of the insula is strong enough to be detected even in small samples. Alternatively, the positive findings described above may reflect type I error, a hypothesis that must be evaluated in additional studies using sufficiently sized samples.

5.2.5. Dorsolateral prefrontal cortex

5.2.5.1. Food paradigms. Activation in dlPFC has been shown to be altered during the processing of food stimuli among individuals with an ED. Acutely ill individuals with AN and BN were shown to exhibit reduced dlPFC activation in response to food images compared to healthy individuals, particularly among individuals with BN (Joos et al., 2011a,b,c; Uher et al., 2004). Interestingly, dlPFC activation was shown to be elevated in response to high calorie food images (Uher et al., 2003) as well as aversive tastes (Cowdrey et al., 2011) among individuals recovered from AN compared to healthy individuals and individuals with acute AN, which may reflect the engagement of regulatory processes that support dietary control. Among individuals with BN, it is possible that reduced dlPFC activation in response to food may underlie periodic loss of control over eating and use of behavioral strategies (e.g., binge eating) rather than cognitive strategies (e.g., reappraisal) to regulate emotions. Less clear is the association between acute AN and reduced dlPFC activation. It is possible that reduced dlPFC activation in response to food may reflect the engagement of avoidance strategies (Table 4). While additional research is necessary to more fully explore the role of the dlPFC in the processing of food stimuli among individuals with EDs, the available evidence provides some initial support for the involvement of this region.

5.2.5.2. Body image paradigms. Alterations in dlPFC activation in response to body image-related stimuli have been documented among individuals with AN in three of 12 studies examining this relationship. Adolescents and adults with AN have been shown to exhibit elevated dlPFC activity when viewing images of themselves distorted to be fat (Wagner et al., 2003). In contrast, adults with AN were found to exhibit reduced dlPFC activation when asked to name the color of words lexically related to fatness compared to healthy individuals (Redgrave et al., 2008). A similar pattern of activation was observed in response to images of participants' bodies distorted to be fat among individuals with BN and restrictive AN compared to healthy individuals and those with AN binge-eating/purging (AN B/P) subtype (Miyake et al., 2010a). It is difficult to explain at a theoretical level why individuals with BN and restrictive AN would exhibit similar dlPFC responses that were not shared by individuals with AN B/P, as AN B/P lies between BN and restrictive AN on the continuum of eating pathology, suggesting that the finding reported by Miyake et al. (2010a) may not reflect true differences in dlPFC responses to distorted body images among individuals with an ED. It is also important to note that the study conducted by Redgrave et al. (2008) was underpowered to detect an effect in the dlPFC, and thus may have observed an effect in this region by chance. Further, Pruis et al. (2012) failed to detect an effect of the dlPFC in planned statistical comparisons using a larger sample. Accordingly, although the dlPFC may play a role in the evaluation of and response to body image stimuli, the available evidence does not provide strong support for this hypothesis (Table 5).

5.2.5.3. Emotion paradigms. Only one of the eight studies examining neural responses to emotional stimuli among individuals with EDs identified a relationship between dlPFC activation and diagnostic status. Women with BN were found to exhibit reduced dlPFC activity while evaluating whether negative traits accurately described them, with the degree of dlPFC activation being negatively correlated with amygdala activation during the task (Pringle et al., 2011). This study was the only study out of the eight that designated the dlPFC as an a priori ROI and conducted analyses to specifically examine whether there were group differences in activation in the dlPFC. Therefore, although none of the other studies identified an effect of dlPFC activation, it is possible that this may be explained by the fact that other studies did not conduct planned comparisons in the dlPFC at the less stringent statistical threshold typically applied in ROI analyses (Table 6). However, positive findings should be interpreted with caution until additional studies are conducted.

5.2.5.4. Reward paradigms. No studies have documented differences in dlPFC activation during reward processing (Table 7). One study failed to do so even when conducting planned comparisons of the dlPFC in a relatively large sample of 40 individuals (Wierenga et al., 2015). As such, the available research suggests that the dlPFC does not participate in reward processing among individuals with an ED.

It is important to note that many of the structural and functional MRI studies in ED populations were likely underpowered to detect effects similar to those observed in MDD (see Table 1). Indeed, none of the structural MRI studies were sufficiently powered to detect effects in the amygdala, VS/NAc, or ACC, and the majority of fMRI studies were underpowered to detect effects in the amygdala, ACC, and insula. It is possible, therefore, that null or discrepant findings regarding the relationship between EDs and the structure and function of these regions may be attributable to inadequate power rather than a true absence of an effect. On the other hand, 97% ($n = 37$) of fMRI studies in ED populations were adequately powered to detect an effect in the VS/NAc, lending some credence to the findings, or lack thereof, reported in this region. Only 53% ($n = 20$) of fMRI studies used samples that were large enough to detect an effect in the dlPFC, making it difficult to determine the extent to which findings in this region are meaningful and reliable. In general, additional studies conducted using larger samples are necessary to resolve inconsistencies in the literature and to provide more reliable evidence of structural and functional alterations in EDs.

6. Discussion

Both MDD and EDs are serious psychiatric conditions that co-occur at a rate higher than would be expected by chance, suggesting that there may be overlapping biological mechanisms influencing risk for both disorders. In support of this hypothesis, there is evidence to suggest that both MDD and EDs are characterized, in part, by impairments in emotion generation and regulation. Though much of this evidence has been drawn from behavioral studies, there is a growing literature documenting that individuals with these diagnoses also exhibit structural and functional differences in the brain regions known to participate in emotion generation

Table 8
Structural abnormalities in brain regions involved in emotion processing and regulation among individuals with Major Depressive Disorder, Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder during acute illness and recovery.

	MDD	Rec MDD	AN	Rec AN	BN	Rec BN	BED	Rec BED
Amygdala	↓	x	↓	x	x	–	–	–
VS/NAc	↓	–	↑ ↓	↑ ↓	↓ (vs. HC & AN)↑ (vs. HC & BED)	–	–	–
ACC	↓	↓	↓	↓	x	–	↑[a]	–
Insula	x	–	↓ ↑	x, ↑	↑	↑	–	–
dlPFC	↓	–	↓ ↑	–	↓	–	–	–

Note. Comparisons are with healthy individuals except where noted. Arrows indicated the direction of reported effects. An x indicates that one or more studies reported no differences between groups. Dashes indicate that there were no studies reporting pertinent findings. MDD = Major Depressive Disorder AN = Anorexia Nervosa; BN = Bulimia Nervosa; BED = Binge Eating Disorder; Rec = recovered; HC = healthy control; VS = ventral striatum; NAc = nucleus accumbens; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

[a] Results based on a single study.

and regulation. Identification of areas of overlap and discordance in the available findings will serve as the basis for evaluating whether alterations in the emotion generation and regulation neurocircuitry are shared by MDD and EDs, and whether such alterations are indicative of a shared etiological mechanism underlying their co-occurrence.

6.1. Similarities across literatures

A careful review of the independent MDD and ED literatures revealed several points of overlap in structural and functional changes in the emotion generation and regulation circuitry. Meta-analytic investigations of structural differences in MDD have revealed that MDD is characterized by reduced volume in the amygdala, striatum, NAc, ACC, and dlPFC. Similarly, individuals with AN have been shown to exhibit reduced volume in each of these regions, though with much less consistency than MDD. Interestingly, amygdala volume reductions appear to normalize with treatment in both MDD and AN, suggesting that amygdala volume may be a state marker of both disorders. Although volume reductions in AN may be secondary to starvation, it is unlikely that starvation fully accounts for these effects given some evidence that volume reductions seem to persist in recovery. Individuals with BN also exhibit reduced striatal volume during the acute phase of illness, providing some evidence that striatal volume reductions may be a cross-diagnostic marker of both disorders. Table 8 provides a summary of structural neuroimaging findings across diagnoses.

It is more difficult to evaluate overlap in functional activation patterns across MDD and EDs given the significant heterogeneity in the tasks used to elicit neural activity and relative lack of studies examining neural responses to affective stimuli among individuals with EDs. Indeed, only nine studies included emotional stimuli in their imaging protocol, and often did so only as a secondary task serving as a comparison to responses elicited during the primary task of interest. As such, the majority of neuroimaging studies conducted in ED populations were not designed to examine how the brain processes emotional information. Moreover, activation in a single brain region may be elicited by a variety of tasks that rely on unrelated processes. As a consequence, it is not possible to determine whether similarities in neural activation patterns across MDD and EDs are reflective of the engagement of similar underlying processes. In addition, many of the studies in the ED literature were conducted in small samples (mean $N = 41$, range = 12–143 across structural and functional studies), and were not always sufficiently powered to detect effects of the size observed in MDD literature. Although it is possible that the effects of brain structure and function in ED populations are larger and thus able to be detected in smaller samples, conducting neuroimaging studies in larger samples of individuals with EDs will be essential for resolving discrepancies in the available literature.

Finally, few ED studies explicitly excluded individuals with comorbid psychiatric illness like depression or individuals taking psychotropic medication, and many did not describe the psychiatric history of participants or their effort to control for the effects of psychiatric comorbidity. Indeed, of the 56 structural and functional neuroimaging papers reporting findings from 52 ED samples, only 17 (30%) specifically excluded individuals with a co-occurring diagnosis of MDD or anxiety disorder. Further, eight of those 17 studies included individuals prescribed antidepressant medication, which might suggest that some of the participants had a history of MDD. It is important to note that the reported findings from the few studies that excluded individuals with a comorbid psychiatric illness did not differ from those using similar tasks that did not do so. Nonetheless, the frequent presence of a comorbid MDD diagnosis within ED samples limits the ability to discern which diagnosis is the primary source of variation in neural outcomes. Further, given the limited number of studies that accounted for psychiatric comorbidity and the significant methodological heterogeneity within the literature (e.g., use of different functional imaging paradigms, focus on different brain regions), it is difficult to draw definitive conclusions regarding the potential impact of co-occurring psychiatric illness. This leaves open the possibility that group differences in regional activation patterns may be partially attributable to the effect of psychiatric comorbidity in participants with EDs rather than being solely attributable to having an ED.

With these important issues in mind, there does seem to be concordance between MDD and AN with regard to amygdala reactivity. Studies examining amygdala activation in MDD have predominantly utilized stimuli with negative affective content, while studies in AN have utilized a broad range of stimuli, including food, body images, and negative affective stimuli. Both disorders have been associated with elevated amygdala activation, though it is unclear if individuals with MDD would exhibit similar increases in amygdala activation in response to food or body images. There is also some overlap in patterns of ACC activation, albeit in a disorder-specific manner. Individuals with MDD exhibit increased ACC activation in response to negative affective stimuli, while individuals with AN or BN exhibit increased ACC activation in response to food cues. Moreover, differences in ACC responses are no longer evident in recovery among individuals with MDD and BN, indicating that altered ACC signaling may be a state marker of acute MDD and BN. A similar, disorder-specific pattern is evident for dlPFC activation, with decreased activation occurring in response to negative affective stimuli among individuals with MDD and in response to food among individuals with an ED. In summary, some structural and functional alterations within the emotion generation and regulation circuitry are shared across MDD and EDs, which might help to explain their co-occurrence.

6.2. Discrepancies across literatures

There are notable discrepancies in structural and functional alterations in the emotion generation and regulation circuitry across MDD and EDs. For example, while insula volume reductions

have been documented in AN, meta-analytic reviews have failed to find a consistent relationship between insula volume and MDD. In addition, individuals with BN and BED exhibit fewer volumetric differences than do individuals with MDD or AN. Those with BN have been found to exhibit greater insula and VS volume, in contrast to the volume reductions in these regions noted in MDD and AN. Individuals with BED have also been shown to exhibit increased ACC volume, which is inconsistent with reductions in ACC volume reported in the primary MDD and AN literatures. These inconsistencies across ED diagnoses may reflect differences in symptom presentation, with BN and BED being characterized by binge eating, a symptom that is less frequently observed in MDD and AN. Alternatively, these discrepancies may be better accounted for by variation in study methodology or the relative lack of pertinent literature applying neuroimaging methodologies to the study of EDs.

As noted previously, few studies have examined neural correlates of emotion generation and regulation in EDs, whereas fMRI studies in MDD have nearly exclusively done so due to the centrality of impaired emotion generation and regulation to MDD. Of those studies in the ED literature that have utilized emotionally arousing stimuli, there is limited evidence of overlap with findings reported in the MDD literature except where described above. Further, sample sizes in the ED literature are fairly small, which may increase error and magnify the effect of confounding variables (e.g., co-morbid diagnoses, length of illness) on the results. However, it is possible that convergent findings might emerge with additional research examining emotion generation and regulation in EDs. Due to the dearth of relevant studies in the ED literature, the lack of consistency across these literatures should not be interpreted as definitive evidence that neural correlates of emotion generation and regulation are not shared across MDD and EDs. Indeed, despite discrepancies across the MDD and ED literatures in the tasks used to elicit neural activity and in the direction of the effects documented in each disorder, the available evidence supports the general hypothesis that both types of disorders are characterized by structural and functional variation in the regions highlighted in this review.

6.3. General limitations

There are many limitations that should be considered when interpreting the evidence reviewed above. First and perhaps most importantly, none of the studies included in this review were specifically designed to examine neural responses during emotion regulation, nor did they manipulate emotion regulation. Thus, the included studies do not directly address the question of whether changes in the neurocircuitry that supports emotion regulation contribute to the co-occurrence of MDD and EDs. Although there are studies in the primary MDD literature that specifically examine neural correlates of emotion regulation, there have been no meta-analyses assessing the strength of reported associations published to date. Within the ED literature, there have been no investigations of the neural correlates of emotion regulation specifically, highlighting an important area in need of additional research. Therefore, while MDD and EDs are characterized by differences in the structure and function of regions that have been implicated in emotion regulation, to conclude that the patterns of activation within these regions documented in MDD and EDs reflect similar processes involves many assumptions that may not be tenable. This is compounded by the fact that there is significant heterogeneity in sampling and experimental methods across studies, making it difficult to compare results within and across the MDD and ED literatures.

Second, longitudinal data are scant, with the predominant use of cross-sectional studies limiting conclusions about causality and state vs. trait characteristics. In the absence of prospective studies that track illness development from the premorbid to recovery phases, it is unclear whether any of the observed differences in brain structure or function reflect preexisting abnormalities that may increase susceptibility for illness, or arise as a consequence of having either MDD or an ED. The lack of longitudinal data is a particular concern for AN, given that starvation during the acute phase of the illness is likely to exert a considerable effect on the structure and function of the brain. Indeed, although the link between starvation and brain atrophy is well documented (Frank, 2015), several studies examining volumetric changes in AN did not account for the effect of starvation by adjusting for group differences in total intracranial volume. Further, while researchers have attempted to disentangle state vs. trait sources of variation by comparing acutely ill individuals to individuals in sustained recovery, the extent to which having MDD or an ED may produce long term or permanent changes in the brain that remain in the "recovered" state is unknown. If present, it is possible that these enduring effects may promote ongoing, but perhaps more subtle, dysfunction, or increase risk for future relapse. Therefore, it will be necessary to build on existing cross-sectional neuroimaging investigations of ill and recovered individuals using longitudinal approaches. Importantly, studies using longitudinal designs have the potential to challenge our current understanding of what constitutes illness and recovery, which may generate novel hypotheses regarding the etiology of these disorders, as well as reveal new avenues for treatment.

Third, much of the reviewed evidence linking MDD and EDs to emotion generation and regulation neurocircuitry was drawn from studies of adults, despite the fact that peak age of onset for both disorders occurs in adolescence or young adulthood (Hudson et al., 2007; Kessler et al., 2005; Lewinsohn et al., 1994). It is well documented that the brain undergoes extensive structural and functional changes during the stages of development in which MDD and EDs tend to first occur (Paus et al., 2008; Raznahan et al., 2011), making it unlikely that illness-related neural abnormalities observed in adulthood will also be evident in adolescence. Importantly, maturation in the neurocircuitry underlying emotion regulation has been associated with improvements in emotion regulation measured behaviorally (McRae et al., 2012). Further, given that earlier age of onset is associated with greater severity and poorer prognosis across psychiatric diagnoses (Kessler et al., 2007), it is probable that the brains of individuals with adolescent onset MDD or EDs will differ markedly from those whose first onset occurs in adulthood. Indeed, research has shown that children and adolescents with MDD differ from their adult counterparts on several neurobiological parameters, including basal cortisol secretion and response to antidepressant medications (Kaufman et al., 2001), as well as in the degree of genetic heritability of depressive symptoms (Waszczuk et al., 2014). Earlier emergence of MDD is also associated with greater subgenual ACC volume (Jaworska et al., 2014), a brain region implicated in emotion regulation and other cognitive processes relevant to psychiatric illness. While no studies examining the neurobiological correlates of EDs have directly compared adults to adolescents, many routinely control for age of onset. Somewhat surprisingly, age of ED onset is not consistently correlated with neural outcomes (e.g. Cowdrey et al., 2011; Cowdrey et al., 2014; Fonville et al., 2013; Friederich et al., 2010; Via et al., 2015), though small sample sizes and methodological heterogeneity likely explain the lack of an association. Finally, despite evidence that illness chronicity is associated with potentially deleterious changes in brain structure and function in both MDD (Dannlowski et al., 2009; Milne et al., 2012) and EDs (Bär et al., 2015; Fonville et al., 2014), duration of illness is not consistently taken into account or reported. In order to advance our understanding of neural mechanisms underlying MDD, EDs, and

their co-occurrence, more systematic investigations of the impact of developmental factors and age of onset are clearly warranted.

Fourth, though not specific to the MDD or ED literatures, whether and how structural characteristics of specific brain regions impact neural signaling within and between regions is not fully understood (Honey et al., 2009). This hinders the integration of structural and functional neuroimaging findings into a more complete understanding of the ways in which various brain regions and networks give rise to processes like emotion regulation. Moreover, this review did not include an exhaustive list of all of the regions involved in emotion generation and regulation, and did not focus on studies that have investigated how these regions function when the brain is not engaged in a specific task. Studies examining interactions between regions were also not considered, though there is mounting evidence that MDD and EDs are characterized not only by regionally specific differences in brain structure and function, but also by differences in the physical and functional connections between regions. Neuroimaging methods that capture network-level connections suggest that complex processes like emotion regulation arise from interactions between brain regions. Therefore, further application of these methods to the study of MDD and EDs may advance our understanding of the neural mechanisms underlying these conditions. Given that each neuroimaging method provides unique information about the brain, future studies would benefit from using a multi-modal imaging approach to assess illness related changes in brain structure and function. Doing so would help to answer questions about how changes in brain structure influence brain function, and how structural or functional changes in a single region influence the properties of the neural networks to which it belongs. Finally, that there are shared alterations in emotion generation and regulation circuitry does not explain why some individuals develop an ED without MDD or MDD without an ED.

6.4. Limitations specific to the ED literature

There are a number of limitations that apply specifically to the ED literature. First, there is debate regarding whether ED subtypes as currently defined represent distinct clinical entities with unique underlying etiologies, or whether they lie along a spectrum ranging from extreme dietary restriction (restrictive AN) to binge eating (BN or BED; Wonderlich et al., 2007). This conundrum is particularly relevant to the classification of AN – binge-eating/purging type (AN – BP) as a distinct diagnostic group, the validity of which has been questioned due to the fact that it shares features with both AN and BN. One approach to addressing this is to examine whether individuals can be accurately classified into their assigned diagnostic group on the basis of brain structure, function, and organization. Although evidence from neuroimaging studies supports the distinction between AN, BN, and BED, only 15 of the 56 reviewed studies included individuals with AN – BP, making it difficult to conduct meaningful comparisons between diagnostic groups. This represents an important area for future research. Similarly, because relatively few studies have been conducted in individuals with BN and BED, it is not possible to draw firm conclusions about emotion generation and regulation in these disorders. It is also unclear whether any of the observed neuroimaging findings apply to males with an ED, as none of the reviewed studies included male participants. Given that the prevalence of EDs is much higher in females (Hudson et al., 2007), it is likely that the mechanisms underlying the development of an ED differ by gender. Further, a significant proportion of men endorse eating disorder symptoms (Striegel-Moore et al., 2009), highlighting the importance of further investigating EDs in males. Finally, many studies of EDs have used disorder-specific stimuli and tasks (i.e., food or body image cues) rather than more general emotion tasks, making it difficult to compare functional differences in EDs with those documented in MDD.

6.5. Future directions

Future studies should examine the neural bases of co-occurring mood and eating problems by including both diagnostic groups in a single study in order to better understand the factors contributing to their co-occurrence. In addition, as noted previously, it will be important to utilize tasks that either involve or manipulate emotion regulation in order to specifically test the hypothesis that signaling variation in emotion generation and regulation circuitry among individuals with MDD and EDs actually corresponds to emotion regulation. It will also be necessary to further evaluate the effects of satiety, hunger, and starvation on emotion regulation and responsivity in the regions highlighted herein, as metabolic state is likely to have an impact on these processes even among healthy individuals (Wagner et al., 2012). Alternatively, it may be fruitful to examine neural correlates of emotion regulation in first-degree relatives of individuals with EDs or other high risk populations so as to remove the confounding effect of starvation while still maintaining an etiologically informative design. Additional research is also needed to evaluate the effect of transient mood states on emotion regulation, eating behavior, and brain activation patterns in a range of populations, including individuals with either MDD or EDs, or both. Longitudinal investigations are necessary to establish a causal relationship between emotion dysregulation and the onset and persistence of MDD and ED symptoms, as well as to determine whether alterations in the neurocircuitry that supports emotion regulation predate the onset of these disorders. Future studies might also consider evaluating the effect of interventions targeting emotion dysregulation on activity in this neurocircuitry, and whether altered neural responses predict symptom remittance. Investigating these important questions about the underlying neural mechanisms linking depression and EDs may ultimately be used to identify novel treatment targets to improve treatment efficacy for both types of disorder.

Declaration of interest

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