Fronto-limbic Neural Activity in Response to Basic Emotion Cues in Adults and Adolescents with Anorexia Nervosa: An fMRI Study

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Abstract

BACKGROUND: Anorexia Nervosa (AN) is a severe mental illness associated with chronicity, poor treatment outcome, high rates of morbidity and mortality, and significant individual and societal costs. Behavioral research studies show that AN is associated with deficits in several aspects of emotional processing, including emotional learning/memory, awareness, recognition, and regulation. It is possible that emotional processing abnormalities, driven by underlying genetic and neurobiological factors, contribute to AN development and persistence. Therefore, better understanding disruptions in basic emotional functioning in AN and the neural correlates that underlie them is critically important. **METHOD**: 19 adolescent and adult females with restricting-type AN (10 medicated, 9 unmedicated) and 19 healthy age and gender matched controls underwent functional MRI in conjunction with an emotional faces task where BOLD response was examined when viewing images of happy and fearful faces (presented in a block design format). Scanning was completed using a 3.0 Tesla scanner. Data preprocessing and analysis was carried out using FEAT in FSL. Whole brain group level analyses were conducted using a mixed-effects model (FLAME) with cluster-wise significant testing (min $Z=2.32$; cluster significance = $p<0.05$, corrected). Between group differences in eight regions of interest (ROIs: bilateral amygdala, insula, pregenual anterior cingulate, and subgenual anterior cingulate) were also examined (MANCOVA). Correlational analyses then investigated the relationships between brain response and self-reported eating disorder symptoms as well as between brain response and participant age. **RESULTS**: Whole brain comparisons showed that, in response to viewing fearful versus happy faces, participants with AN had lower activation in areas of the pregenual

anterior cingulate and ventral prefrontal cortex. When examining ROIs, participants also showed reduced activity in pregenual anterior cingulate regions, which remained when controlling for body mass index and self-reported depression and anxiety. Findings did not appear to be a consequence of psychotropic medication use. Greater severity of eating disorder, depression, and anxiety symptoms was associated with lower activation in left ventral prefrontal regions. In addition, brain response in the left insula correlated with participant age and measures of eating disorder severity. No significant correlations were observed between clinical data and other ROIs, including the amygdala.

CONCLUSION: Findings from the current study suggest that, during the ill state of restricting-type AN, fearful facial expressions elicit decreased functional activity in anterior cingulate and ventral prefrontal regions, areas of the brain that are central to emotional processing. Disruptions in neural activity may contribute to deficits in emotional awareness, recognition, and unconscious emotional regulation which have been widely observed within behavioral studies in AN. Future research is needed to further examine how fronto-limbic deficits in this disorder may be related to disease vulnerability and symptom maintenance. Such studies may guide identification of treatment targets and development of novel interventions, which are severely limited in this disorder.

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1. Anorexia Nervosa, an Introduction

Anorexia nervosa (AN) is a serious mental illness that is often chronic and relapsing in nature. It is associated with high rates of morbidity and mortality as well as significant impairments in functioning, reduced quality of life, and high individual and societal costs. Treatment options for AN are severely limited, due in part to a limited understanding of factors that cause and maintain AN symptoms. Compared to other areas of psychopathology, neurobiological correlates of AN are severely understudied. Although research has begun to examine the underlying neurobiology of the disease, investigations focused on exploring central processing of basic emotions in this disorder leaves a major gap in the literature, especially given that deficits in emotional functioning have been hypothesized as potential factors contributing to AN development and persistence. Research aimed at improving our understanding of the neurobiological underpinnings of emotion processing deficits in AN is especially important as it has the potential to identify treatment targets and guide the development of novel intervention and prevention strategies for this chronic, often debilitating disorder.

This paper begins with a detailed description of the AN phenotype including epidemiological data, information about disease course and outcome, and a discussion about the relationship between genetics and general emotional functioning in AN. An in-depth review of behavioral research suggesting that AN is associated with emotional processing deficits is then provided followed by the description of a novel study that directly examines the neurobiological correlates of basic emotion processing among adolescent and adult women with this illness.

1.1. The AN Phenotype

1.1.1. Cardinal Symptoms

AN is a severe psychiatric illness involving ego syntonic, self-driven starvation and emaciation, an intense fear or refusal to gain weight, body image disturbance and an overvaluation of shape and weight towards one's self-concept (American Psychiatric Association, 2013). Low-weight status in AN is achieved through extreme dietary restriction and can also involve other maladaptive behaviors including binge eating and purging (e.g., self-induced vomiting), over exercise, and abuse of laxatives, diuretics or other substances. [Note: although the previous edition of the DSM (DSM-IV-TR) required the presence of amenorrhea (or the cessation of at least three menstrual cycles) in order to make the diagnosis of AN, this criterion has been eliminated from the current diagnostic manual based on research suggesting its lack of clinical utility and specificity (Dalle Grave, Calugi, & Marchesini, 2008; Mitchell, Cook-Myers, & Wonderlich, 2005; Wilfley, Bishop, Wilson, & Agras, 2007)].

1.1.2. Prevalence & Incidence

Average point prevalence rates of AN in females in western countries (using previous DSM-IV criteria) range from 0.29% - 0.39% (American Psychiatric Association, 2000; Hoek, 2006), with lifetime prevalence rates between 0.90 - 2.2% (Bulik et al., 2006; Favaro, Ferrara, & Santonastaso, 2003; Hoek, 2006; Hudson, Hiripi, Pope, & Kessler, 2007; Lewinsohn, Striegel-Moore, & Seeley, 2000; Wade, Bergin, Tiggemann, Bulik, & Fairburn, 2006), rates comparable to other chronic mental illnesses such as Obsessive Compulsive Disorder, Schizophrenia, and Bipolar Disorder (American Psychiatric Association, 2013; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Although substantially lower than that for females, lifetime prevalence rates for AN in

males are estimated at 0.24 - 0.30% (Hudson, Hiripi, Pope, & Kessler, 2007; Raevuori et al., 2009). Prevalence rates are notably higher when subthreshold cases of the disorder are considered (Lewinsohn et al., 2000; Wade et al., 2006; Walters & Kendler, 1995) and are also greater (upwards of 4%) when considering newer DSM-5 diagnostic criteria over older DSM-IV-TR criteria (Allen, Byrne, Oddy, & Crosby, 2013; Bulik et al., 2006; Smink, van Hoeken, & Hoek, 2012).

Estimates from epidemiological studies suggest that, in Western European countries, the incidence (number of *new* cases in the population per year) of severe AN increased rapidly between 1960 and 1970 and have since plateaued (Milos et al., 2004; Smink et al., 2012). In the United States, incidence rates in older women and in males have remained stable over time, but have steadily increased among young females 15-24 years of age (between the 1935 to 1989 survey period; Lucas, Crowson, O'Fallon, & Melton, 1999). It is unclear whether this rising incidence in younger females reflects better detection of the illness or an earlier age of onset (Smink et al., 2012). Regardless, methodological limitations (e.g., overreliance on psychiatric case registries or hospital records) plague the most rigorous epidemiological studies, where calculated incidences rates are generally considered to be underestimates (Hoek, 2006).

1.1.3. Gender, Race, & Ethnicity

As previously noted, AN is more prevalent in females than males at a ratio of approximately 10:1 (Hoek & van Hoeken, 2003; Hudson, Hiripi, Pope, & Kessler, 2007; Lucas et al., 1999; Smink et al., 2012). The presence of AN is likely under-detected in males due, in part, to societal stigma and males' reluctance to identify with an illness that is typically associated with women (Raevuori et al., 2009).

Although lower than what is typically observed in Caucasian women within the U.S., AN has been observed among African Americans (Taylor et al., 2013) as well as among individuals of Latino/Hispanic (Alegria et al., 2007) and Asian decent (Nicdao, Hong, & Takeuchi, 2007); however, risk factors, presentation, and course of the illness vary based on racial and ethnic background (Franko, 2007; McKnight Investigators, 2003). As Hoek (2006) points out, very few epidemiological studies of AN have been conducted outside of the United States or Western European countries. Nonetheless, cases of AN have been observed in Malaysia (Buhrich, 1981), Japan, China (Tsai, 2000), Iran (Nobakht & Dezhkam, 2000), the Caribbean (Hoek, Van Harten, Van Hoeken, & Susser, 1998) and "in every non-Western region of the world" (Keel & Klump, 2003).

1.1.4. Age of Onset, Course of Illness, & Prognosis

AN typically develops during adolescence and often follows a protracted, chronic course (Golden, 2003). Long-term follow-up studies indicate that, although full recovery is possible, approximately two thirds of individuals with AN continue to relapse or suffer prolonged illness (Eckert, Halmi, Marchi, Grove, & Crosby, 1995; Fichter, Quadflieg, & Hedlund, 2006; Herzog et al., 1999) associated with significant impairment, morbidity, and death (Becker, Grinspoon, Klibanski, & Herzog, 1999; Fichter & Quadflieg, 1999; Steinhausen, 2002).

1.1.5. Morbidity & Mortality

Psychological comorbidity is present in over half of AN cases where anxiety and depressive disorders are particularly common (Hudson, Hiripi, Pope, & Kessler, 2007; Steinhausen, 2002). Similarly, somatic complications including osteoporosis, cardiovascular disturbances, diabetes, thyroid disorders, gastrointestinal disorders,

infertility, and pregnancy problems are often reported (Erdur et al., 2012; Meczekalski, Podfigurna-Stopa, & Katulski, 2013). In addition, meta-analyses have indicated that anorexia nervosa is associated with the highest mortality rate among all mental disorders and is three times higher than that for depression, schizophrenia, or alcoholism (Harris & Barraclough, 1998). Estimates suggest that the rate of death in AN as 6-14 times higher than that in the general population due to both medical complications associated with the disease as well as suicide (Arcelus, Mitchell, Wales, & Nielsen, 2011; Crow, Praus, & Thuras, 1999; Herzog et al., 2000; Meczekalski et al., 2013; Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). Twenty percent of individuals with AN who die do so by suicide (Arcelus et al., 2011). On account of the substantial morbidity and mortality associated with these illnesses, the World Health Organization has designated eating disorders as a global health priority within adolescent mental health (WHO, 2003).

1.1.6. Treatment & Costs

A majority of individuals with AN in the community never enter the mental healthcare system (Hoek, 2006). For those that do, treatment effectiveness, especially in adults with AN, is severely limited (Bulik, Berkman, Brownley, Sedway, & Lohr, 2007). There is no medication approved for the treatment of AN, and aside from Family Based Treatment (FBT) for adolescents, it remains uncertain what psychotherapeutic approach might work best (Carter et al., 2011; Watson & Bulik, 2012). Low treatment-seeking phenomena and a lack of effective treatment options contribute to the disorder's chronic course, frequent relapse, and high treatment cost (Attia, 2010).

The disease burden of AN is high. In addition to psychiatric and medical complications, AN is associated not only with reduced quality of life (Winkler et al.,

2014), but with significant social, occupational, and economic/healthcare costs (Keilen, Treasure, Schmidt, & Treasure, 1994; Mond, Hay, Rodgers, & Owen, 2009; Simon, Schmidt, & Pilling, 2005). Additionally, AN is among the top ten leading causes of disability among young women (Mathers, Vos, Stevenson, & Begg, 2000). In a study examining National Health Service data from April 1999 to March 2000, Thompson et al. (2004) reported that eating disorders were associated with the longest (median) hospital stays among psychiatric disorders. Similarly, Striegel-Moore (2008) has noted that eating disorders have greater healthcare utilization compared to individuals with other forms of mental illness.

1.2. Genetics, Neurobiology & Emotion in AN

Socio-cultural factors, such as the idealization of thinness and a dominant dieting industry, have long been associated with eating disorder pathology (Garner & Garfinkel, 1980; Miller & Pumariega, 2001; Pate, Pumariega, Hester, & Garner, 1992; Rubinstein & Caballero, 2000); however, evidence of deliberate self-starvation reminiscent of current-day AN cuts across historical time period (possibly dating back to medieval times) and cultural climate (Keel & Klump, 2003). According to a series of meta-analyses and literature reviews, this strongly suggests that AN is not merely a culture-bound syndrome (Keel & Klump, 2003).

1.2.1. Genetics in AN

Data from twin and family studies suggest that AN has a strong genetic component. Eating disorders aggregate in families, where lifetime risk of AN in first-degree relatives of an affected individual is ten times higher than that of an unaffected individual (Bulik, Slof-Op't Landt, Van Furth, & Sullivan, 2007; Lilenfeld et al., 1998).

This makes AN among the most familial of all mental illnesses (Kaye et al., 2008). There is also cross-transmission of AN and Bulimia Nervosa (BN) within families, suggesting that familial risk for eating disorders is not illness-specific (Strober, Freeman, Lampert, Diamond, & Kaye, 2000).

In a population-based twin sample drawn from the Minnesota Twin Family Study, genetic factors accounted for 74% of the variance in broadly defined AN (full and subthreshold AN; Klump, Miller, Keel, McGue, & Iacono, 2001). Subsequently, a larger population-based twin study in Sweden for more strictly defined AN concluded that 57% of variance in the syndrome was due to genetic influence (Bulik et al., 2010). These findings converge with those reported in earlier twin studies drawn from clinical populations (Holland, Hall, Murray, Russell, & Crisp, 1984; Holland, Sicotte, & Treasure, 1988).

Molecular genetic studies (i.e., linkage and association studies) have started to examine the underlying genetic basis of AN. Linkage studies, non-a priori methods which attempt to identify regions of DNA associated with particular traits, are far from identifying strong candidate genes for AN (Bulik, Slof-Op't Landt et al., 2007); however, areas of chromosomes 1, 2, 4, and 13 have all been associated with the AN phenotype (Trace, Baker, Penas-Lledo, & Bulik, 2013). This part of the genome codes for numerous genes, many of which are known to be expressed in the brain (Bulik, Slof-Op't Landt et al., 2007) and includes genes that align with established theories of AN neurobiology. In addition, although association genetic studies in AN are limited, generally underpowered, and tend not to replicate, polymorphisms among serotonin (5-HT), dopamine, and Brain-Derived Neurotropic Factor (BDNF) genes show particular promise (Bergen et al., 2003;

Bergen et al., 2005; Brown et al., 2007; Kaye, Frank, Bailer, & Henry, 2005; Ribases et al., 2003; Ribases et al., 2005) especially as alterations in these particular neurotransmitter systems have been well documented in AN.

1.2.2. Neurotransmission in AN

A detailed description of functional neuroimaging studies (e.g., fMRI) that have been conducted examining neural circuitry in AN is provided below in section 2.2.2 of this paper (e.g., The State of Neuroimaging in AN); however, a brief discussion regarding our understanding of neurotransmitter functioning in this disorder is warranted here given the role of neurotransmission in emotional experience more generally. There is evidence that, compared to healthy control groups, concentrations of serotonin metabolites in cerebral spinal fluid (CSF) and serum concentrations of BDNF are decreased during acute phases of AN (Hashimoto, Koizumi, Nakazato, Shimizu, & Iyo, 2005; Kaye et al., 2005; Nakazato et al., 2009). Conversely, individuals who have recovered from AN show increased and decreased concentrations of serotonin and dopamine metabolites in CSF respectively (Kaye, Frank, & McConaha, 1999; Kaye et al., 2005). Converging studies investigating neurotransmitter receptor activity using Positron Emission Tomography (PET) and Single-Photon Emission Computerized Tomography (SPECT) technologies show that AN is associated with increased serotonin (5-HT) 1A and dopamine D2/D3 receptor binding as well as reduced binding of serotonin (5-HT) 2A receptors (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013). Functional alterations in serotonin and dopamine receptor activity persist following recovery from AN (Frank 2005, Kaye 2008), suggesting that they likely exist premorbidly as well as during the ill state of the illness.

1.2.3. Neurotransmission & Emotion in AN

The neurotransmitter systems noted above play an important role in many altered systems in AN including appetite, weight regulation, motor activity, and reward (Kaye et al., 2005; Kaye et al., 2013; Kernie, Liebl, & Parada, 2000); however, they are critically important to emotional functioning. Serotonin and dopamine receptors are concentrated in areas of the limbic system, which is known to control emotions (Cooper, Bloom, & Roth, 2003; Kaye, 2008; Kaye et al., 2013). Additionally, BDNF polymorphisms linked with the AN phenotype have been associated with depression and high trait anxiety (Groves, 2007) as well as increased reactivity to emotional stimuli (Montag, Reuter, Newport, Elger, & Weber, 2008).

Clinically, patients with AN report that they engage in eating disorder behavior, in part, to help manage intense emotions, reports which are also supported by findings in the wider literature (Brockmeyer et al., 2012; Engel et al., 2013; Kaye et al., 2013; Steinglass et al., 2010). The transdiagnostic theory of eating disorders purports that dysfunctional eating disorder behaviors (e.g., self-starvation, binge eating, self-induced vomiting) function to reduce or neutralize negative mood states, which, through negative reinforcement, serve to further maintain these illnesses (Fairburn et al., 2009). It is possible that hypersensitivity to emotional experiences in AN, driven by underlying genetic and neurobiological factors, creates a vulnerability to the illness and perpetuates its symptoms. Better understanding disruptions in core emotional functioning in AN is, therefore, especially important, as they might be factors contributing to AN risk and maintenance.

1.3. Background Summary

Taken together, it is clear that AN is a serious mental illness associated with chronicity, poor treatment outcome, increased mortality, and significant costs. Family and twin studies show that AN is a highly heritable illness. Although future research focusing on more homogeneous AN endophenotypes will likely yield more fruitful information about the direct genetic basis of this heterogeneous, complex syndrome (Bulik, Slof-Op't Landt et al., 2007), studies thus far suggest that genetic factors in the disorder may exert their influence through the expression of genes that control neurobiological systems central in emotional processing. Numerous self-report and behavioral studies, as described in the next section of this paper, show that processing of emotions is highly disturbed in AN and might be a particularly important factor contributing to the illness. As Steinhausen (2002) points out in a large review of the literature, the field has not made significant progress in regards to improving the outcome of AN over the last half century, possibly due to continued uncertainty about etiological and maintenance mechanisms in the disorder. Therefore, empirical studies that advance our understanding of the emotional processing deficits underlying AN are critically needed in order to better guide development of effective strategies that reduce the personal and societal burdens of this disease.

2. Emotions in Anorexia Nervosa: A Review of the Literature

This section begins with a description of early observations of emotional functioning in AN followed by an in-depth literature review of behavioral research showing that AN is associated with deficits in several aspects of emotional processing. The relationship between fronto-limbic neural circuitry in the brain and emotional functioning is discussed, followed by a description of the current state of functional

neuroimaging research in AN that suggests disruptions in emotion circuitry exist among those with the disorder. A novel study that directly examines the neurobiological bases of emotion deficits in this illness is then described.

2.1. Emotion Processing in AN

2.1.1. Observations of Emotions in AN

Deficits in emotional processing have been hypothesized as a factor contributing to AN development and maintenance since its earliest descriptions. For instance, emotion processing and regulation difficulties were first noted in AN in 1873 when Lasegue, the French neuropsychiatrist thought to have discovered the syndrome, described young women with anorexia as "suffering from some emotion which [s]he avows or conceals" (as summarized by Vandereycken & van Deth, 1990). Hilde Bruch, an early expert in eating disorders and obesity, noted that women with AN have a deficiency in the ability to identify emotional states, feel easily overwhelmed by their emotions, and struggle to differentiate physical sensations from emotional experiences (Bruch, 1962).

More recent studies note that individuals with AN are characteristically anxious (Kaye, Bulik, Thornton, Barbarich, & Masters, 2004), harm avoidant (Klump et al., 2000), fearful of uncertainty (Frank et al., 2012), hypersensitive to feedback (Jappe et al., 2010), and exhibit high levels of negative emotionality (Lilenfeld, Wonderlich, Riso, Crosby, & Mitchell, 2006; Pike et al., 2008). Emotional difficulties typically predate AN onset and tend to persist following recovery, suggesting that they create a vulnerability to eating disorder development (Cassin & von Ranson, 2005; Kaye et al., 2013; Wagner et al., 2006). As noted by Kaye (2013), these characteristics "may constitute an intermediate phenotype between genes and vulnerability to AN".

Emotional processing, generally, can be used as an umbrella term to describe numerous components of emotional behavior including emotional learning, emotional awareness and perception, emotional recognition, and emotional regulation (Gilboa-Schechtman, Avnon, Zubery, & Jeczmien, 2006; Ochsner, 2008). Behavioral research studies have documented that *all* of these components of emotional processing appear altered in AN. Findings from these studies will now be discussed.

2.1.2. Emotional Learning & Conditioned Bias

One of the most fundamental aspects of emotional processing involves conditioned reward learning, where individuals associate emotionally-laden stimuli with positive or negative outcomes (Ochsner, 2008). Problems with conditioned learning lead to attentional/memory biases for certain emotional cues and is often measured using dot-probe, incidental learning, and Stroop tasks. Similar to other emotional disorders (Power & Dalgleish, 1997), attentional and memory biases for emotional stimuli have been observed in AN. [Note: this review is focused primarily on emotional processing generally; therefore research solely investigating bias towards emotionally-salient but disease-specific (e.g., food, weight, body size) stimuli is not described in detail here, although it has been well-documented in the literature (Dobson & Dozois, 2004; Johansson, Ghaderi, & Andersson, 2005)].

Dot-probe tasks present two stimuli side-by-side on a screen (e.g., a neutral and negative emotion word) that disappear and are followed by a visual cue in the same location as one of the previously presented stimuli. Response latency to the cue's location is used as a measure of attentional bias. Quicker response times are thought to reflect greater attention to the stimulus item presented in the same location as the subsequent

cue. Using this type of task, Rieger et al. (1998) found that, compared to healthy female controls, individuals with eating disorders had quicker response times (and thus demonstrate biased attention) towards negative (e.g., fat, angry) and away from positive body-related and emotional words (e.g., thin, happy).

Within group comparisons from incidental word-learning tasks have shown that female AN inpatients freely recall more negatively valenced nouns compared to neutral words (Suslow et al., 2004). In this experiment, target words (various adjectives) and distractor words (positive and negative nouns, e.g., friend, crisis) were presented on a computer screen. Participants were asked to attend to and describe the valence of the target adjectives only, but were then asked to freely recall the distractor words. The proportion of positive, negative, and neutral distractor words recalled was quantified as a measure of unplanned associative learning and memory (aka, emotional memory bias). Additionally, using a conditioned-association paradigm, Murph, Nutzinger, Paul, & Leplow (2002) found that individuals with AN made more errors when learning associations between neutral words and abstract geometrical shapes compared to both HC and individuals with BN. There were no differences in error rates between groups when learning to associate threatening words with shapes. Authors suggest that this reflects a within group bias in AN, where they are less attentive to non-threatening words than those that are more emotionally salient.

Attentional bias towards negative emotional cues has been further demonstrated in AN using modified versions of the Stroop Task. In these tasks, different words or images (e.g., threatening versus neutral) are displayed in various colors on a computer screen. Participants are asked to ignore the content of what is presented and name only

the color of the cue as quickly as possible. Longer response times to color naming are thought to reflect attentional bias due to greater difficultly inhibiting automatic processing of the meaning or significance of content in the presented cue (Cisler, Bacon, & Williams, 2009; Stormark & Torkildsen, 2004). Employing use of a modified Stroop Task in individuals with eating disorders (i.e., AN and BN) and healthy controls, Stormark and Torkildsen, (2004) assessed bias towards not only disease-specific (i.e., food) stimuli, but more general emotional stimuli. Negative emotional words (e.g., death, shame, anxiety, sick) and pictures (e.g., a child with deformities or injuries) were compared to neutral words (e.g., day, meter) and images (e.g., hammer, sofa). In addition to delayed response times for food-related stimuli, this study indicated that individuals with eating disorders had longer color naming latencies for both negative emotional words and pictures compared to neutral stimuli. Although this study did not look at AN specifically, others employing modified Stroop Tasks presenting angry or neutral facial expressions compared to non-face stimuli (e.g., chairs) have shown that individuals with AN, specifically, demonstrate biased attention towards angry-threatening faces compared to control groups (Harrison, Tchanturia, & Treasure, 2010), which is independent of current levels of anxiety or depression. Similar findings exist among other eating disorders (Harrison, Sullivan, Tchanturia, & Treasure, 2010) and in individuals following recovery from AN (Harrison et al., 2010), suggesting that attentional biases are present across the eating disorder spectrum, are likely trait-related, and possibly a factor contributing to disease risk and maintenance.

These studies described above suggest that AN is associated with conditioned bias towards negative emotional information; however, other studies have questioned the

direction of this bias. Jansch, Harmer, and Cooper (2009) have noted that individuals with AN respond more slowly to and remember fewer self-referent emotional words than healthy comparison groups. This study used a categorization task, where participants quickly grouped positive (e.g., interesting, pleasant) and negative (e.g., selfish) personality traits based on the degree to which they would like to be described by each trait. Incidental emotional memory/learning was further examined by asking participants to freely recall as many previously presented self-referential emotion words as possible. No group differences were observed during control conditions that had participants categorize and recall neutral words (e.g., animals), suggesting that deficits in AN are specific to emotional information and not reflective of slower processing speeds or impaired memory more generally. Findings in this study do not clearly indicate whether individuals with AN demonstrate biases towards or against negative emotions per se, but could suggest avoidance of emotional information directed at themselves, regardless of valence.

As Oldershaw (2011) notes, attentional bias in eating disorders is complex. Findings regarding the direction of bias and whether it exists between groups or within AN specifically depends on the task being employed; however, taken together, studies indicate that previously reported biases towards illness-specific stimuli (e.g., food, body shape) appear to extend to more basic emotional information in AN as well, particularly information that is negative or threatening in nature.

2.1.3. Awareness & Perception of Emotion in Oneself

After affective learning takes place and the value of an emotional stimulus has been encoded as something to either approach or avoid, it is important that an individual

is able to identify and react quickly to similar stimuli later on. Adaptive emotional responding involves the ability to perceive emotional processes within oneself and to accurately recognize emotions of others. Because identification of one's own emotions involves self-awareness, this section begins with a discussion of self-report studies of alexithymia, which has been extensively studied in eating disorder populations, followed by a description of experimental and objective measures of emotional perception in AN.

2.1.3.1. Alexithymia. The alexithymia construct involves impairments in the conscious awareness of emotions (Subic-Wrana, Bruder, Thomas, Lane, & Kohle, 2005), particularly the ability to pinpoint, differentiate, and describe emotional experiences (Nemiah & Sifneos, 1970; Sifneos, 1973; Taylor, Bagby, & Parker, 1991). Typically measured with versions of the Toronto Alexithymia Scale (TAS-20 or TAS-26), a widely used measure with well-tested reliability and validity (Kupfer, Brosig, & Brahler, 2000; Taylor, Bagby, & Parker, 2003), numerous studies have documented greater levels of self-reported alexithymia in both adult and adolescent eating disorder samples compared to non-symptomatic controls (Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007; Cochrane, Brewerton, Wilson, & Hodges, 1993; Corcos et al., 2000; Eizaguirre, Saenz de Cabezon, Ochoa de Alda, Olariaga, & Juaniz, 2004; Schmidt, Jiwany, & Treasure, 1993; Subic-Wrana et al., 2005; Taylor, Parker, Bagby, & Bourke, 1996; Zonnevijlle-Bender, van Goozen, Cohen-Kettenis, van Elburg, & van Engeland, 2002; Zonnevylle-Bender et al., 2004), especially on subscales measuring deficits in emotional identification and emotional expression (Kessler, Schwarze, Filipic, Traue, & von Wietersheim, 2006; Taylor et al., 1996; Zonnevylle-Bender, van Goozen, Cohen-Kettenis, van Elburg, & van Engeland, 2004). Positive associations have also been reported between alexithymia and

eating disorder variables (i.e., self-report scores on the Eating Disorder Inventory) in non-clinical samples (Laquatra & Clopton, 1994). This increased alexithymia appears to negatively predict outcome independent of baseline eating disorder severity or depressive symptoms, where patients with greater difficulties identifying emotions at baseline are more symptomatic and show less symptom improvement after 3 years (Speranza, Loas, Wallier, & Corcos, 2007).

While some studies note no differences in alexithymia between different eating disorder diagnoses (Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007; Cochrane et al., 1993; Kessler et al., 2006; Zonnevijlle-Bender et al., 2002), others have found that individuals with AN are more alexithymic than those with bulimia nervosa (Bydlowski et al., 2005; Corcos et al., 2000; Eizaguirre, Saenz de Cabezon, Ochoa de Alda, Olariaga, & Juaniz, 2004; Schmidt et al., 1993). These self-report findings have been found to correlate with outside observer (i.e., parent/partner) ratings of alexithymia (Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007), providing corroborating evidence for the presence of abnormal emotion processing in this population.

Greater alexithymia in AN is not associated with age, education level, use of psychotropic medication, nor does it appear to be related to markers of illness severity, namely body weight or duration of illness (Bourke, Taylor, Parker, & Bagby, 1992; Bydlowski et al., 2005; Kessler et al., 2006; Laquatra & Clopton, 1994; Parling et al., 2010; Schmidt et al., 1993). In addition, although starvation dampens physiological feedback and could impair emotional awareness (Miller, Redlich, & Steiner, 2003), greater alexithymia is also observed in parents of individuals with AN compared to those without symptomatic children, suggesting that difficulties with identifying and describing

emotions are not a consequence of impaired cognition due to starvation or prolonged malnutrition and are thus a trait increasing vulnerability to AN development (Eizaguirre, Saenz de Cabezon, Ochoa de Alda., Olariaga, & Juaniz, 2004; Taylor et al., 1996); however, this conclusion must be made with caution. First, although alexithymia in AN is associated with ineffectiveness and interpersonal distrust (other traits common among individuals with eating disorders), it is not directly related to eating behavior or attitudes about weight and shape (Taylor et al., 1996). In addition, alexithymia has also been found in other mental illnesses including substance use disorders, post-traumatic stress disorder, panic disorder, and somatoform disorders, where the TAS-20, in particular, does not differentiate between different psychiatric diagnoses (Subic-Wrana et al., 2005; Zonnevylle-Bender et al., 2004; Zonnevylle-Bender et al., 2004). Additionally, alexithymia, as measured by the TAS-20, has been consistently correlated with depression measures both in clinical and general population studies (Bydlowski et al., 2005; Cochrane et al., 1993; De Groot, Rodin, Olmsted, 1995; Eizaguirre, Saenz de Cabezon, Ochoa de Alda, Olariaga, & Juaniz, 2004; Hintikka, Honkalampi, Lehtonen, & Viinamaki, 2001; Kessler et al., 2006; Parker, Bagby, & Taylor, 1991; Zonnevylle-Bender et al., 2004). Factor analysis of the TAS-20 and Beck Depression Inventory-II have also shown that, while depression and alexithymia loaded on separate factors in a large, general community sample (N=1888), the underlying factor structure differed and had greater overlap when limiting the examination to a subset of the population self-reporting high levels of both alexithymia and depression (Hintikka et al., 2001).

It is not hard to see how measurement of alexithymia could be influenced by concurrent depression, which is highly comorbid with AN (Hudson, Hiripi, Pope, &

Kessler, 2007). For example, depression leads individuals to view themselves in a more negative, self-critical manner, where one might rate themselves as deficient in a particular domain (e.g., per the TAS-26, "I am able to describe my feelings easily") even in the absence of an objective impairment. While Bourke et al. (1992) failed to find differences in alexithymia between individuals with AN reporting high versus low levels of depression and others have similarly reported higher alexithymia in AN patients without a co-morbid mood disorder compared to controls (Eizaguirre, Saenz de Cabezon, Ochoa de Alda, Olariaga, & Juaniz, 2004), increased alexithymia in AN tends to disappear when statistical analyses control for continuous (vs. dichotomous) measures of depressive symptomology (Corcos et al., 2000; Parling et al., 2010), which also occurs when concurrent anxiety is taken into account (Parling et al., 2010). However, in adolescents, alexithymia measured by the TAS-20 has remained increased in AN compared to controls even when depression severity is entered as a covariate (Parling et al., 2010).

Therefore, while research consistently shows that individuals with AN believe they possess deficits in their own emotional awareness and expression, it is possible that self-reported alexithymia in AN is driven by underlying negative affect and reflective of general distress shared among several disorders, not specific to eating disorder pathology. To better understand emotional processing deficits more unique to AN and to circumvent the challenges with questionnaire measures of alexithymia, other efforts have employed the use of performance-based measures of emotional awareness that are less confounded by comorbidity.

2.1.3.2. Levels of Emotional Awareness Scale (LEAS). Questionnaire measures of alexithymia, such as the TAS-20, ask individuals with supposed difficulties accessing and

communicating their emotional experience to, paradoxically, report on their lack of emotional awareness and diminished capacity to describe feelings. This is inherently problematic. Therefore, the LEAS, a performance-based measure of alexithymia, was developed to better assess emotional processing deficits in psychiatric groups who may not be able to accurately reflect on and report these deficits using self-report methods. The LEAS measures emotional awareness by analyzing the verbal contents of participants' descriptions of 20 short stories that depict various emotional situations between two people. The presented scenarios were designed to pull for four types of emotions: anger, fear, happiness, and sadness. Following presentation of each vignette, participants are asked to write responses to two questions: "How would you feel?" and "How would the other person feel?" The measure is scored using structured criteria based on the degree to which specific physiological, behavioral, and emotional reactions are reported (greater emotional complexity reflects higher scores). In other words, the LEAS asks participants to put feelings into words in the moment, not just to reflect on their beliefs about their own emotional abilities in more general situations (as pulled for with alexithymia self-report measures). Of note, this measure has been shown to be independent of depression and anxiety (Bydlowski et al., 2002; Bydlowski et al., 2005; Lane, Quinlan, Schwartz, Walker, & Zeitlin, 1990). Additionally, it accounts for more variance in emotional recognition ability than does self-report alexithymia measures (Lane, Sechrest, & Riedel, 1998). According to Lane and Schwartz (1987), alexithymia is a lower level cognitive-emotional process compared to emotional awareness, which is developmentally more complex and defined as the ability to describe one's *current* emotional state as well as the emotional experiences of others.

In a well-powered study using the LEAS, Bydlowski et al. (2005) noted that emotional awareness (both on subscales assessing awareness of oneself and others) was significantly impaired in a mixed, treatment-seeking eating disorder group compared to controls. Between diagnostic groups, emotional awareness was particularly poor in AN compared to those with BN. Although individuals with AN demonstrated good to superior verbal skills (Mathias & Kent, 1998), they appeared to have difficulty describing emotional experiences specifically. Another study, also employing the LEAS, noted that emotional awareness in oneself self was significantly lower in individuals with acute AN compared to controls, although no differences existed in regards to participants' ability to identify emotional experiences in others (Oldershaw, Hambrook, Tchanturia, Treasure, & Schmidt, 2010). These findings were independent of participant age, education level, psychotropic medication use, concurrent depression and anxiety, duration of illness, BMI, or severity of eating disorder symptoms (Bydlowski et al., 2005; Oldershaw et al., 2010). Although low LEAS scores among those with eating disorders persist following 8-12 weeks of pharmacological and psychodynamic treatment (Subic-Wrana et al., 2005), investigations have noted that impairments in emotional awareness are not present in samples of longer-term recovered AN (Oldershaw et al., 2010). Together, findings suggest that deficits in emotional awareness, particularly within oneself, are specific to the current disease state but are not a function of comorbid psychopathology. As noted by Oldershaw et al. (2010), these studies are consistent with investigations that have described emotional awareness deficits as a maintenance factor and negative prognostic indicator in AN (Speranza et al., 2007), where state changes in the illness (e.g., nutritional deficiencies) may interact with and facilitate emotional difficulties (Miller et

al., 2003). Conversely, improvements in this domain might assist with the recovery process.

2.1.3.3. Emotional Perception. In addition to LEAS, other experimental studies of emotional perception have shown that AN is associated with a disconnect between changes in physiological arousal and subjective emotional experience. Similar to the LEAS, these studies improve upon self-report measures of alexithymia and reduce the degree of needed reflection and retrospective recall bias. Miller et al. (2003) recorded physical stress (measured by changes in heart rate) and self-reported affect (measured with a continuous visual analogue scale) in adolescents with AN compared to healthy controls within the context of a stress-inducing speech task. Compared to healthy adolescents, the AN group had lower physiological arousal overall, but greater levels of reported distress and anxiety; however, relative increases in heart rate in response to the stress-induction task in those with AN corresponded with reported decreases in negative affect. In a follow-up study employing the same methods, partially and fully weight restored individuals with AN (75-104% ideal body weight) had similar patterns of autonomic arousal compared to controls in response to stress induction, but self-reported greater sustained levels of negative affect throughout the task (Miller, Erickson, Branom, & Steiner, 2009).

Zonnevylle-Bender et al. (2005) measured self-reported emotion, heart rate and salivary cortisol before and after a stressful speech task and found that adolescents with AN reported significantly higher levels of negative emotion in response to stress, but lacked a corresponding increase in cortisol or heart rate seen in controls. Authors noted that the lack of physiological reactivity in AN was not due to hypercorticolism, HPA

down regulation, or low blood glucose levels, nor were findings a result of psychiatric medication use. Together, these studies suggest that AN is associated with an incongruence between ones' physiological and emotional state, where difficulties with interoceptive awareness and the ability to link bodily cues with emotional reactions are observed. However, these studies did not account for psychiatric co-morbidity, so it is unclear whether differences in self-reported affect are specific to eating disorder symptomology or reflect general psychological distress (e.g., depression).

In addition to studies examining correspondence between physical arousal and self-reported emotional experience, Joos, Cabrillac, Hartmann, Wirsching, and Zeeck (2009) investigated differences in perception of basic emotions between patients with AN, BN, and healthy controls when confronted with emotionally-laden visual images. Scenic pictures as well as images of faces from the International Affective Picture System (IAPS) were presented to participants who rated the degree to which they personally experienced emotions of fear, anger, happiness, and sadness (using a 7-point Likert scale ranging from 1, "very low" to 7, "very high") in response to each image. Compared to both BN and healthy controls, AN was associated with increased fear perception when confronted with pictures meant to elicit anger. These findings were present even after controlling for depression. Using the same methods, Joos et al. (2011) investigated disorder specific patterns of emotional perception in a larger sample of individuals with eating disorders compared to depressed patients and controls. They found that individuals with both eating disorders and depression perceived experiencing less anger than the healthy comparison group in response to anger eliciting images, which was independent of depression severity. Authors suggest that findings reflect difficulties

coping with anger in interpersonal situations among those with AN, which may not be specific to ED pathology.

Alterations in emotion perception within oneself extend beyond those with a clinical eating disorder and are also observed in non-clinical populations. Harvey, Troop, Treasure, and Murphy (2002) noted that women without eating disorders who report high levels of eating concerns are more reactive to visual stimuli eliciting fear (e.g., aggressive faces, snarling dog) and disgust (e.g., disfigured image) compared to those with low eating concerns, even when controlling for individual differences in emotional sensitivity. In this study, individuals reported the degree to which they experienced fear and disgust on a 10-point visual analogue scale (ranging from "not at all true" to "very true") following presentation of emotional images.

Overall, self-reported alexithymia is evident in AN, although measurement of this construct via questionnaires is inherently problematic. However, performance-based measures that are less sensitive to psychiatric comorbidity provide evidence that awareness and perception of ones' own emotions are impaired in the ill state of AN and might be related to disease persistence. Difficulty identifying and processing one's own emotions likely interferes with the ability to accurately recognize and understand emotions in others, which has further been noted in the AN literature.

2.1.4. Recognition of Emotion in Others

Emotional recognition is, thus far, the most well researched domain of emotion processing in the eating disorder literature, and has been investigated in AN using a variety of methods. In the Reading the Mind in the Eyes (RME) task, 36 different images of human eyes are presented on a computer screen and participants have to choose one of

four different emotional states that best describes what is expressed in each image. Eating disorder groups, generally, are less accurate at identifying emotions on this task compared to controls, despite demonstrating comparable basic visual processing abilities (Russell, Schmidt, Doherty, Young, & Tchanturia, 2009). Deficits are significantly worse in restricting-type AN versus BN (Harrison et al., 2010). Impaired emotional recognition measured by the RME negatively correlates with self-report measures of emotion regulation, where those with decreased capacity to recognize emotions in others is associated with greater difficulties managing one's own emotional responses (Harrison, Sullivan, Tchanturia, & Treasure, 2009). Additionally, Harrison et al. (2010) have noted that both recovered and ill AN are less accurate at identifying emotions on this task compared to controls, suggesting that poor emotional recognition may be a trait-like factor in AN. These findings are not associated with BMI, duration of illness, or self-reported symptoms of depression and anxiety (Russell et al., 2009).

Reading the Mind in Voice and Film (RMV, RMF) tasks are similar to the RME, in that they assess participants' ability to recognize and infer emotional states in others. Stimuli in these tasks are audio recordings of short sentences varying in content and intonation (RMV) as well as short film clips of social scenes (RMF). Individuals judge the emotional content of these stimuli by choosing the best affective descriptor from multiple-choice options displayed on a computer screen. Consistent with RME, individuals with AN demonstrate greater difficulty accurately identifying emotions from voices and from visual scenes compared to healthy controls (Oldershaw et al., 2010), findings which are also observed in individuals with sub-clinical eating disorder symptoms (Ridout, Thom, & Wallis, 2010). Poor accuracy is observed in AN both in

regards to identification of negative and positive emotions (Oldershaw et al., 2010).

Several studies have investigated recognition of basic emotions using full human faces. Findings conform with those noted above and provide additional evidence for altered emotional processing in AN. For example, adults with AN correctly identify fewer emotions, misclassify more emotions, and are slower to respond than healthy controls on the Facial Expression Recognition Task (FERT; Jansch et al., 2009). On this task, participants are asked to categorize various intensities of 6 basic emotions (sad, fear, angry, happy, disgust, surprise) in others as quickly as possible on a computer screen. Similarly, when briefly (i.e., 2 seconds) presented with pictures of emotional expressions, mixed eating disorder samples as well as adolescents with restricting-type AN demonstrate greater difficulty free-labeling and making forced decisions about presented emotions compared to age and gender matched controls (Zonnevijlle-Bender et al., 2002; Zonnevylle-Bender et al., 2004). These studies all includ a series of cognitive (i.e., verbal fluency) and non-emotional categorization/recognition tasks to show that performance differences with regard to emotional stimuli are not a consequence of general processing deficits secondary to malnutrition or prolonged illness (Jansch et al., 2009; Zonnevijlle-Bender et al., 2002; Zonnevylle-Bender et al., 2004). Pringle, Harmer, and Cooper (2010) lend further support to this claim, noting that female dieters (i.e., those at risk for disordered eating who do not meet clinical criteria for a diagnosis) also demonstrate decreased accuracy when categorizing facial expressions, where poorer task performance predicts greater disordered eating attitudes.

While some have failed to find differences in performance between different emotions in AN (Jansch et al., 2009), others have reported greater deficits recognizing

"surprised" facial expressions (Kessler et al., 2006), neutral faces (Pollatos, Herbert, Schandry, & Gramann, 2008), and more negatively valenced emotions such as fear, sadness, and disgust (Kucharska-Pietura, Nikolaou, Masiak, & Treasure, 2004; Pollatos et al., 2008).

In a meta-analysis combining studies noted above, medium-sized effects (with no publication bias) in recognition difficulties between AN and controls have been observed (Oldershaw et al., 2011). Converging lines of evidence thus suggest that the ability to recognize emotions in others among those with AN is impaired. Additionally, these deficits exist in adolescent and adult samples, extend to sub-clinical and recovered populations, and are not due to medication use, depression severity or alexithymia (Pollatos et al. 2008).

2.1.5. Emotion Regulation

In addition to impairments in emotional learning, awareness, perception, and recognition as described above, individuals with AN also appear to struggle with emotional regulation, conceptualized as the ability to manage, influence, and effectively control one's own emotional experience (Harrison et al., 2009). This construct has been assessed in eating disorder samples, primarily with the Difficulties with Emotion Regulation Scale (DERS: Gratz & Roemer, 2004). The DERS is a 36-item self-report measure quantifying difficulties in emotional management across 6 domains: 1) lack of emotional clarity, 2) lack of emotional awareness, 3) non-acceptance of emotional responses, 4) impulse control difficulties in response to negative emotions, 5) difficulties engaging in goal-directed behavior when upset, and 6) limited access to emotion regulation strategies. These domains capture subjective emotional experience as well as

self-identified abilities in regards to differentiating, altering and attenuating emotions. (Note: the first two domains overlap with alexithymia constructs, whereas the remaining four domains more directly assess self-regulation and control).

Overall, adult AN samples self-report significant impairments in emotion regulation across all subscales of the DERS compared to healthy comparison groups (Brockmeyer et al., 2012; Harrison et al., 2009; Manuel, Wade, Manuel, & Wade, 2013; Merwin et al., 2013). Similar findings are observed in adolescent samples, in more broadly-defined patient samples (e.g., those with subthreshold AN), and remain significant when controlling for concurrent depression (Manuel et al., 2013). According to Manuel and Wade (2013), negative affective memory bias mediates differences between clinical diagnosis and DERS score, accounting for 30% of the total effect of AN diagnosis on emotion regulation difficulties. This pattern suggests that negative affective memory bias might serve to maintain problems with emotion regulation in AN.

In addition to studies employing the DERS, other self-report measures, namely the Response Styles Questionnaire (RSQ; Nolen-Hoeksema & Morrow, 1991) and the Negative Mood Regulation Scale (NMR; Catanzaro & Mearns, 1990) have been used in eating disorder samples. The RSQ quantifies the tendency to ruminate or adaptively distract when distressed whereas the NMR captures self-confidence in regulating negative mood. Adults with AN report significant impairments on both scales compared to control groups, findings which are mediated by concurrent distress levels (Gilboa-Schechtman et al., 2006).

2.1.5.1. Eating Disorder Behavior as a Regulation Strategy. Given observations of emotion processing deficits in AN, several investigators have hypothesized that eating

disorder behavior functions as a maladaptive means of coping with emotional impairments or difficult emotional experiences. This idea has been well studied in BN. For example, using ecological momentary assessment (EMA), which allows for investigation of temporal relationships between events in the natural environment, Smyth et al. (2007) have shown that binging and purging (e.g., self-induced vomiting) are predicted by increases in negative affect over time whereas engaging in BN-behavior serves to decrease negative mood. More recent studies have extended this type of work to AN. In a large, multi-site study of adult AN, Engel et al. (2013) asked participants to report on momentary affect, loss of control eating, purging, exercise, drinking fluids to curb appetite, and self-weighing multiple times per day for two weeks using a hand-held computer. Information on food restriction was also collected daily during the study window. Similar to findings in BN, negative affect increased prior to binging, purging, and self-weighing in AN and subsequently decreased following these behaviors. Negative affect also decreased following exercise and consuming fluids aimed at curbing appetite. Restricting eating behavior is inherently more difficult to study using EMA methods because, unlike purging for example, is not as discrete of a behavior. However, authors noted that higher daily ratings of negative affect were associated with a greater likelihood of food restriction the following day. Together, these findings suggest that eating disorder behavior in AN (and BN) functions to modulate negative mood states and is maintained on account of its negative reinforcing properties.

According to Merwin et al. (2013) restrictive eating behaviors, specifically, might develop as a means to diminish or avoid discomfort associated with sensory/emotional hypersensitivity. Recovery from AN, on the other hand, might require improvements in

the ability to cope more adaptively with intense emotions and sensations. These conclusions were drawn from a study comparing healthy controls to both ill and recovered (i.e., weight-restored) women with AN. They noted that both patient groups demonstrated self-reported hypersensitivity to sensory stimuli, a proxy for emotional experience; however, individuals recovered from AN reported better emotion regulation abilities whereas acute AN was associated with emotion dysregulation (across all DERS subscales; Merwin et al., 2013). Others have noted that emotion regulation difficulties differ between acute AN groups and controls, but not between recovered AN and comparison samples (Harrison, Tchanturia et al., 2010), further indicating that emotion regulation problems remit and may be required for successful recovery. Compared to depressed samples, participants with AN report fewer impairments in emotion regulation skills (although both groups demonstrate impairments compared to controls), which suggests that, albeit maladaptive, individuals with acute AN might attribute eating disorder behaviors (e.g., dietary restriction) to effective emotional coping strategies (Brockmeyer et al., 2012).

2.1.6. Summary of Emotion in AN: Self-report & Behavioral Studies

Converging evidence from self-report and behavioral studies support early observations in AN that indicate the illness is associated with abnormal emotional processing. Specifically, AN groups exhibit conditioned attention and memory biases for emotional information that is primarily negative or threatening in nature. Although self-report studies of increased alexithymia in AN are complicated by comorbid depression and anxiety, performance based behavioral studies that are less influenced by current levels of psychiatric distress show that individuals with AN have difficulties being aware

of/perceiving emotions within themselves and accurately recognizing emotions in others. Lastly, individuals with AN self-report difficulties with emotion regulation, where eating disorder behaviors seem to function as a maladaptive strategy aimed at modulating negative mood states and emotional sensitivity. Several studies indicate that emotional processing abnormalities are present across the eating disorder spectrum, are likely trait-related, and possibly a factor contributing to disease risk and maintenance. Despite evidence from self-report and behavioral studies, very little is known about the neurobiological processes that underlie and drive these emotion processing deficits observed in AN.

2.2. Neural Correlates of Emotion Processing

2.2.1. Fronto-limbic Brain Circuitry

Emotional experiences, as described in the review above, are highly complex, multi-dimensional phenomena that involve both bottom-up (e.g., emotion perception/recognition) and top-down (e.g., emotion regulation) neurobiological processes. Fronto-limbic neural circuitry is comprised of neocortical, subcortical and paralimbic brain structures that all interact to regulate emotional experiences and affective behavior (Mayberg, 1997; Seminowicz et al., 2004). Specifically, neocortial structures (e.g, dorsal-lateral prefrontal cortex, cingulate cortex, medial prefrontal cortex) play a regulatory role in emotion processing (Halari et al., 2009) whereas paralimbic structures (e.g., insula, amygdala, hippocampus) form the foundation of our emotional system responsible for reacting to emotional cues (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Ochsner, 2008). In particular, the amygdala is central to the development of conditioned fear responses (Morris, Ohman, & Dolan, 1998), the detection of threat,

and the recognition of emotions in faces or eyes (Adolphs, Tranel, & Damasio, 1998; Baron-Cohen et al., 2000; Phillips, Drevets, Rauch, & Lane, 2003a). The anterior insula and ventral regions of the anterior cingulate cortex have reciprocal connections with the amygdala (Augustine, 1996) and play a major role in identification of the significance of emotional cues and in the conscious awareness of emotions (Phan, Wager, Taylor, & Liberzon, 2002; Phillips, Drevets, Rauch, & Lane, 2003a).

2.2.2. The State of Functional Neuroimaging in AN

Compared to other areas of psychiatric research (e.g., psychosis, depression), relatively few studies have investigated neurobiological aspects of eating disorders (Frank, Bailer, Henry, Wagner, & Kaye, 2004). In AN, functional MRI studies investigating fronto-limbic neural circuitry have received some attention in the literature, almost exclusively examining brain response to emotionally laden food and body-related stimuli. Findings suggest that greater amygdala and insula activity is present in AN participants when viewing food images (Ellison et al., 1998; Joos et al., 2011). In addition, according to meta-analytic studies, individuals with AN show increased activation in bilateral middle frontal and right anterior cingulate cortices (Zhu et al., 2012) when viewing pictures of food compared to healthy controls, where middle frontal hyperactivity is present even in individuals recovered from AN (Uher et al., 2003). In response to body-related stimuli (i.e., words describing shape/weight, images of body figures), activation has significantly differed between AN patients and healthy controls within numerous fronto-limbic regions including the insula, anterior cingulate cortex (Friederich, Brooks, Uher, Campbell, Giampietro, Brammer, Williams, Herzog, & Treasure, 2010), dorsal-lateral prefrontal cortex (Redgrave et al., 2008), medial frontal

cortex (Vocks et al., 2011), and amygdala (Miyake et al., 2010; Seeger et al., 2002; Vocks et al., 2010).

Overall, these studies suggest that activation in fronto-limbic brain regions is altered during the presentation of emotionally charged, disease-relevant cues, where these studies have most frequently implicated hyperactivity in the amygdala, insula, and anterior cingulate cortex. While this is important to help us understand the neurobiological correlates of core cognitive and behavioral AN symptoms, the field has paid little attention to the study of neurobiological features underlying basic *emotional* processing in this disorder. This is surprising given that deficits in emotion processing have been, as reviewed above, well-documented in the behavioral literature and are hypothesized to be a factor contributing to AN development and maintenance since its earliest descriptions. Therefore, in order to better understand whether emotional processing abnormalities in AN observed in behavioral studies are related to *general* aberrations in fronto-limbic circuitry, Hatch et al. (2010) have suggested that studies that employ the use of more innate emotion cues, such as facial expressions, are needed in the context of fMRI.

To date, only one known study has looked at functional brain activity in response to emotional facial expressions in AN with fMRI methods. Cowdrey, Harmer, Park, and McCabe (2012) examined whole-brain and regional (i.e., amygdala, fusiform gyrus) differences in activation among 16 unmedicated adults recovered from AN compared to 16 healthy controls when viewing happy and fearful expressions. Only individuals considered to be medically and psychologically recovered were included in this investigation. Specifically, AN participants had to have had a BMI between 18.5-25

kg/m^2, regular menses, and be free from psychoactive medications for the last year. In addition, they had to score within one standard deviation of community norms for the Eating Disorder Examination Questionnaire, a widely used measure of eating disorder severity. No differences were observed between the two groups, where the authors concluded that impairments in emotional face processing are not present after symptom remission and are thus not a trait-related phenomenon. However, it is important to note that this study employed the use of a low-powered magnet (1.5 T), which may not have had the resolution necessary to detect small changes in brain activity between groups. Region of interest analyses, which may have been able to more closely examine response to emotional faces in specific brain regions, did not include fronto-limbic regions aside from the amygdala. Therefore, this study is limited in its ability to draw conclusions about functioning within wider emotion-processing networks. Additionally, Cowdrey et al. (2012) did not include an acutely ill group in their study, so it remains unclear whether neural functioning differentiates acutely ill patients with AN from healthy controls and whether this reflects, specifically, a neurobiological mechanism of disease maintenance as suggested by Hatch et al. (2010).

The lack of neuroimaging studies specifically focused on basic emotion processing in acute AN leaves a substantial gap in the literature that, once addressed, could improve our understanding of the neurobiological bases of emotion processing abnormalities in this disorder and help guide treatment development or identify treatment targets.

3. Fronto-limbic Neural Activity in Response to Emotion Cues in Adults and Adolescents with Anorexia Nervosa: An fMRI Study

A new study will now be described that builds on behavioral research reviewed above and expands upon previous neuroimaging findings in recovered AN in order to more thoroughly understand neurobiological functioning associated with emotion processing deficits during acute phases of the illness. This project employed the use of functional neuroimaging technology in conjunction with a widely used emotional faces task. Specific aims of this study were to: 1) to characterize brain activity within fronto-limbic neural circuits in response to happy and fearful emotional expressions among adolescents and adults ill with AN compared to healthy controls, and 2) to characterize the relationship between neural activity and eating disorder symptoms (i.e., dietary restraint).

Given findings from previous neuroimaging studies in AN, the amygdala, insula, and anterior cingulate cortex were chosen as specific fronto-limbic regions of interest for this study. It was hypothesized that individuals with AN would exhibit hyper amygdala activity in response to fearful facial expressions when compared to age-matched controls, reflective of an emotional hypersensitivity to negative emotional stimuli. Consistent with fMRI studies suggesting heightened anterior insula and cingulate activity in response to disease-related cues, it was also expected that functional activity within these regions would be greater for individuals with AN compared to healthy controls, reflective of wider emotional processing aberrations in those with restrictive eating behaviors. Lastly, it was hypothesized that eating disorder symptoms (i.e., dietary restraint) would be associated with brain response to fearful faces in the AN group, providing indirect evidence that emotion processing abnormalities function as a maintenance mechanism for

eating disorder behavior in AN. Exploratory analyses were also conducted to examine the role of development in eating disorder symptoms and brain response.

4. Methods

4.1. Participants

Thirty-eight adolescent and adult females (19 with AN and 19 healthy age and gender matched controls, HC), ages 16-30 years old (M = 22.63, SD =3.73), were recruited to participate in this study. Participants were predominately Caucasian (91.9%), never married (94.6%), and full-time students (64.9%). 54.3% had completed undergraduate and/or graduate studies. Study inclusion and exclusion were determined by an extensive screening process, which included an initial phone screen, in-person diagnostic interviews, and a battery of self-report questionnaires (see Measures). Inclusion criteria for both groups included: 1) being of the female gender; 2) between 16-30 years old; 3) able to read and write in English; and 4) able and willing to attend two in-person study visits including a one-hour MRI scan. Additional exclusion criteria for both HC and AN groups included the following: 1) current substance abuse or dependence; 2) history of serious head injuries, neurological disorders, or medical instability; 3) MRI contraindications (e.g., metal implants, pacemakers, claustrophobia); and 4) currently pregnant or breastfeeding. Healthy controls had to be free from any current or lifetime eating disorder diagnosis. Individuals in the AN group were required to meet DSM-5 criteria for AN with underweight status (Criterion A) being defined as body mass index (BMI) $\leq$ 18.5. In order to reduce heterogeneity within the sample, only participants who met current DSM-5 criteria for the restricting subtype were enrolled, although 21.0% of the AN group reported a past history of binging and 31.6% reported a

history of self-induced vomiting. Average duration of illness was 8.11 years (*SD*=4.42). Use of psychotropic medication was permitted and used by 53% (*n* = 10) of the AN sample at the time of the study. Additionally, 53 percent of the AN sample was receiving outpatient or residential mental health treatment, and 37% of the AN sample reported a history of at least one psychiatric hospitalization. To increase the representativeness of the AN group, psychiatric co-morbidity was permitted, although individuals with a history of bipolar disorder or schizophrenia were excluded from study participation. Diagnostic criteria for mood and anxiety disorders were not formally assessed; however, self-report measures were used to evaluate co-morbid psychiatric symptoms, which were subsequently included in data analyses. Demographic, symptom, and treatment history data are presented in table 1.

4.2. Measures

4.2.1. Symptom Assessments

Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1995). This study employed the SCID-I/P, a semi-structured clinical interview that assesses for current and lifetime DSM-IV-TR Axis 1 disorders (full and subthreshold). This instrument is considered a "gold standard" diagnostic measure with moderate to excellent inter-rater reliability (Lobbestael, Leurgans, & Arntz, 2011). For this study, only the initial screening, eating disorder, and substance use modules of the SCID-I/P were used. This allowed for the assessment of basic inclusion and exclusion criteria, while also reducing the overall assessment burden for participants. Criteria assessed in the SCID-I/P were modified to conform with current

DSM-5 standards for a diagnosis of AN (i.e., those with BMI ≤ 18.5 and without amenorrhea were included in the AN patient group).

Eating Disorder Examination, Version 16.0 (EDE; Fairburn, 2008). The EDE is a clinician-administered, semi-structured interview that is widely utilized in eating disorder research. This instrument served as the primary measure of ED pathology for this study. The EDE assesses frequency of eating disorder behaviors (i.e., binge eating, self-induced vomiting, laxative misuse, diuretic misuse, and excessive exercise) and provides information needed to make diagnostic determinations. This instrument also provides a summative global score reflecting severity of core cognitive features associated with eating disorder pathology, which is comprised of 4 subscales: Dietary Restraint, Eating Concerns, Shape Concerns, and Weight Concerns. Individual items are rated on a 7-point Likert scale (higher numbers reflective of greater pathology) and then averaged to produce subscale scores. The global score is further comprised of the average of subscale scores. Normative values for the EDE have been compiled using community samples (Global Score, M=0.93, SD=0.80; Fairburn & Beglin, 1994). Although specific diagnostic items include the past 3 months, overall and subscale items are assessed over the past month (i.e., 28 days). The EDE has been shown to accurately differentiate between eating disorder cases and non-cases (criterion-oriented validity) and correlates with other measures of eating disorder pathology (construct validity; Berg, Peterson, Frazier, & Crow, 2012). Additionally, the EDE has well-documented test-retest and inter-rater reliability as well as good internal consistency across all 4 subscales (Berg et al., 2012).

Eating Disorder Questionnaire, Version 9.0 (EDQ; Mitchell & Peterson, 2005). The EDQ is a database-like instrument where self-reported information is collected about the following: demographics, weight history, body dissatisfaction, eating disorder symptoms, psychiatric history, medical history, mental health treatment history, menstrual history, medication use, and family medical/psychiatric history. It is a useful tool often employed in eating disorder research that provides a wealth of background data on each participant. Primary items of interest for this study included self-reported demographic information and psychiatric history.

Beck Depression Inventory, second edition (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a 21-item self-report questionnaire that measures severity of depressive symptoms (within the last week). Each item is rated on a 0-3 scale with a maximum total score of 63. Total scores between 0-13 indicate minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (Beck, Steer, Ball, & Ranieri, 1996). Given the population of interest in the current study, participants were asked an additional follow-up question to the item assessing weight loss. Specifically, they were asked to indicate whether or not they have been "purposely trying to lose weight by eating less." If participants answered affirmatively to this question, weight loss as assessed by the BDI-II was scored as absent. This was done to avoid the issue of primary eating disorder symptoms inflating current depression scores. The BDI-II is a widely used instrument in psychiatric research and has been shown to have adequate concurrent validity and high ($a = .91$) internal consistency (Beck et al., 1996).

State-Trait Anxiety Inventory (STAI; Spielberger, 1983). The STAI is 40-item self-report measure that assesses both state (e.g., "I feel calm") and trait-related anxiety (e.g., "I worry too much over something that really doesn't matter", "I am a steady person"). Participants rate each item based on how they 1) currently feel (state items) or, 2) how they are generally (trait items) using a 4-point Likert scale ranging from 1, ("not at all") to 4, ("very much so"). Nineteen total items are reverse-scored (e.g., "I feel calm"). Each scale (i.e., state and trait) ranges from 20-80, with higher scores indicating greater anxiety. Significant evidence suggests that this measure has construct and concurrent validity (Spielberger, 1989). Internal consistency of scale items ranges from 0.86-0.95 and test-retest reliability has been shown to range from 0.65-0.89 (Spielberger, 1983).

Toronto Alexithymia Scale (TAS; Taylor, Ryan, & Bagby, 1985). The TAS is a 26-item self-report questionnaire assessing 1) difficulty identifying and describing feelings, 2) difficulty distinguishing feelings from bodily sensations, 3) concrete and reality based thinking, and 4) reduced daydreaming. Participants are asked to rate the degree to which they agree or disagree with each item on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). Items are summed, with higher numbers reflective of greater alexithymia. Eleven total items are reverse-scored (e.g., "When I cry I always know why"). Total scores range from 26-130, with a score $\geq$ 74 indicating the presence of alexithymia. The TAS possesses a stable factor structure, good construct and criterion validity as well as internal consistency and test-retest reliably (Bagby, Taylor, & Parker, 1988; Bagby, Taylor, Parker, & Loiselle, 1990; Cochrane et al., 1993; Taylor & Bagby, 1988; Taylor et al., 1988).

4.2.2. Behavioral Paradigm (Emotional Faces Task)

All participants completed a 5.2 minute Emotional Faces Task in conjunction with a functional MRI scan where standardized grayscale images of adult men and women with either fearful or happy expressions were presented in a block design format and contrasted with fixation blocks (Ekman & Friesen, 1976). Images were presented on a screen placed at the back of the MRI scanner and then projected to participants by 2 mirrors attached to the head coil. The order of item presentation consisted of 13 24-second blocks [5 fixation (C), 4 happy (H), 4 fearful (F) presented in a counterbalanced fashion (CFHCHFCHFCFHC)]. During experimental blocks, fearful or happy images were presented for 200 msec and followed by 1300 msecs of either a fixation cross or an "o". During control blocks, fixation crosses were presented sequentially for 1500 msec. Emotional facial expressions are efficient at eliciting response in fronto-limbic areas (Fusar-Poli et al., 2009), may be particularly sensitive to emotional processing biases (Stuhrmann, Suslow, & Dannlowski, 2011), and have been extensively studied in other areas of psychopathology including depressive (Arnone et al., 2012; Suslow et al., 2010; Tao et al., 2012; Yang et al., 2010) and anxiety disorders (Beesdo et al., 2009; El Khoury-Malhame et al., 2011). While facial expressions presenting numerous negative emotions have been shown to activate the amygdala (Fitzgerald et al., 2006), a key area of interest in this study, fearful stimuli were chosen because, 1) fear has long-been viewed as important in AN and is included within the diagnostic criteria for the illness (American Psychiatric Association, 2013), and 2) research has suggested that amygdala response is more sensitive to viewing fearful faces than sad faces (Fusar-Poli et al., 2009; Sheline et al., 2001). Happy faces were chosen as a comparison condition over neutral

faces in order to maximize the contrast in brain response and given previous research suggesting that neutral faces can be interpreted negatively (Maniglio et al., 2014).

4.3. Image acquisition

Scanning was conducted with a research-dedicated 3 Tesla Siemens TIM Trio scanner at the University of Minnesota Center for Magnetic Resonance Research. A 32-channel radio-frequency (RF) head coil was used to obtain images for all participants. A high-resolution anatomical image was collected for each participant using a T1-weighted magnetization prepared gradient echo sequence (MPRAGE: 224 coronal slices, TR = 2530 msecs; TE = 3.65 msecs; TI = 1100 msecs; flip angle = 7^{o} ; FOV = 256; voxel size = 1x1x1 mm isotropic; matrix size = 256x176). Task-based functional data were acquired using the Human Connectome Project multiband echo planar imaging sequence (MB-fMRI) where 294 T2*-weighted whole brain functional volumes (64 contiguous slices; TR = 1320ms; TE = 30 msecs; flip angle = 90^{o}, FOV = 212 mm; voxel size = 2x2x2 mm; matrix = 106x106; multiband factor = 4; PE = P>A) were obtained in conjunction with the emotional faces task. A 10-volume resting-state functional scan with comparable parameters except for an opposite phase encode direction (PE = A>P) was collected for purposes of dewarping functional data during preprocessing steps.

4.4. Procedure

Participants with AN were recruited from The Emily Program, a residential and outpatient treatment facility for eating disorders within the Twin Cities and from community advertisements. Healthy controls were recruited from flyers posted throughout the Minneapolis and St. Paul metro area. This study was approved by the University of Minnesota Institutional Review Board.

Interested participants underwent an initial phone screening to assess for basic inclusion and exclusion criteria. Those who appeared eligible were scheduled for a screening visit where they received additional study information, signed informed consent forms, and completed diagnostic and behavioral assessments (i.e., self-report questionnaires). For participants under 18 years of age, parental consent and adolescent assent were obtained. Participants were weighed using a digital scale and had their height measured using a standard stadiometer during their first study visit. Body mass index was calculated for each participant based on height and weight data (kg/m^2). Graduate level assessors conducted the SCID-I/P and EDE interviews with participants to further assess eligibility criteria and determine eating disorder diagnoses. All study assessors were formally trained on administration of study instruments, which included direct observation and participation in mock interviews to ensure proficiency. Weekly assessment meetings with licensed clinicians were held during the study period where assessment-related questions were discussed and resolved.

Enrolled participants then completed a subsequent study visit consisting of the MRI scan at the University of Minnesota Center for Magnetic Resonance Research, where both anatomical and functional images (i.e., in response to the Emotional Faces Task) were collected. Prior to scanning procedures, participants completed a pregnancy test, which was required to be negative to proceed with the study. Participants were instructed to remain still throughout the scan to ensure quality data acquisition. During the Emotional Faces Task, participants held a response pad in their right hand and were told to press a response key with their pointer finger any time the ‘o’ symbol appeared on the screen. This was done to ensure that participants were viewing all the stimuli and that

they remained attentive throughout the task. Following the MRI scan, all participants received compensation for completing study procedures.

4.5. Statistical Analysis

4.5.1. Power

In a previous study using the same emotional faces fMRI task, a large effect (d=0.93) was observed in regards to amygdala response between individuals with depression and healthy controls (Jappe et al., 2014). According to power analyses (G-Power), the sample size in the current study (N=38) was expected to similarly detect large effects given a ß=0.80 and α=0.05. However, Desmond and Glover (2002) note that general power calculators do not accurately estimate power for neuroimaging analyses because they do not take into account intra *and* inter person variability in BOLD % signal change. Following simulation studies, these authors concluded that N=24 is needed to achieve adequate power in fMRI studies while taking into consideration the need for multiple comparison correction. In addition, procedures that increase signal to noise ratio (SNR), such as the multi-band imaging sequence used the current study, reduce intra-subject variability and increase the effect size observed, making adequate power more attainable with smaller sample sizes. Although studies have yet to examine brain function in response to emotional facial stimuli in current AN vs. HC (which makes the current study particularly novel), neuroimaging research in AN, including studies with positive findings within fronto-limbic brain regions, tends to include sample sizes ranging from N=6 to N=35 (Friederich et al., 2010; Mohr et al., 2010; Seeger et al., 2002; Strigo et al., 2013; Uher et al., 2004; van Kuyck et al., 2009). Given this information, a sample size of N=38 was deemed both reasonable and feasible for the current study.

4.5.2. Demographics and Clinical Data

Demographic and clinical variables were analyzed using a series of Independent Samples T-tests and Fisher's Exact Test in SPSS (Version 19.0). Fisher's Exact Test was used instead of Chi-squared tests due to low frequency categorical data. For Independent Sample T-tests, assumptions of normality were evaluated using Shapiro Wilk Test as well as inspection of Q-Q plots, skewness, and kurtosis. Levene's Test was used to assess homogeneity of variance between groups and Welch's T-test was used when unequal variances were observed. Mann-Whitney U tests were used when assumptions of normality were violated. For measures of central tendency, group means and medians were presented for Independent Sample T-tests and Mann-Whitney U tests respectively. (Note: two-tailed tests were used with significance level set at alpha=0.05).

4.5.3. Functional Data

Imaging data were processed and analyzed using the FEAT package in FSL 4.1.9 (www.fmrib.ox.ac.uk). Preprocessing steps began with brain extraction (BET) and motion correction (MCFLIRT). Functional data were visually inspected for movement-related artifacts. Specifically, volumes with relative displacement (based on MCFLIRT translation numbers that calculate mean change in position between adjacent volumes) in excess of 0.5 mm ($1/4^{th}$ voxel) in any direction were removed. Single volumes preceding and following excess displacement were also removed from analysis. In total, very few total volumes were excluded on account of excessive motion (12 total volumes, or 0.1%). Spatial smoothing (FWHM 5mm), high-pass temporal filtration (Gaussian-weighted least squares straight line fitting, sigma = 100s), and regression of motion parameters were subsequently completed as part data preprocessing. EPI images were co-registered with

each individual's anatomical image (brain extracted and visually inspected for quality) and then normalized to Montreal Neurological Institute (MNI) standard space with FNIRT. All neuroimaging analyses were conducted using a 2-step approach. A first level GLM analysis regressed the model specified by the emotional faces task onto the blood oxygen level dependent (BOLD) response of each participant. This model yielded four separate contrasts for each participant that were then entered in later stages of analysis: fear > fixation, happy > fixation, fear > happy, and happy > fear. Second level, whole brain group analyses were then conducted using a mixed-effects model (FLAME). Cluster-wise significant testing was used where multiple comparison corrections were carried out using Gaussian random field theory (min $Z=2.32$; cluster significance = $p<0.05$, corrected). Group level analyses produced z-score maps for comparisons between stimuli conditions.

Average z-scores for each individual within predetermined regions of interest (ROIs) were extracted using Featquery for further between-group comparisons. The Harvard-Oxford Subcortical Structural Atlas was used to extract activation values from bilateral amygdala. Talairach Daemon Labels (Lancaster et al., 2000) were used to identify activity within subenual cingulate, pregenual cingulate, and insular regions. Multivariate analyses of covariance (MANCOVA) were used to assess group differences in ROIs, with group status as the fixed factor and BOLD response as the dependent variable. Research has shown that depression and anxiety severity as well as body weight status influence functional activity within fronto-limbic brain regions (Hall et al., 2014; Hattingh et al., 2013; Killgore & Yurgelun-Todd, 2005; Stein, Simmons, Feinstein, &

Paulus, 2007). Therefore, to control for this, de-meaned BMI and scores from the BDI and STAI were added as covariates in later stages of both whole brain and ROI analyses.

Additionally, psychotropic medications have been shown to alter fronto-limbic function (Tanti & Belzung, 2010), specifically within the amygdala (Sheline et al., 2001; Tao et al., 2012) as well as emotion processing of fear specifically in eating disorder samples (Jansch et al., 2009). Therefore subsequent analyses examined the four contrasts between HC and the unmedicated and medicated AN subgroups separately.

Follow-up correlational analyses were run to examine associations between demographic/clinical variables and BOLD response both within significant clusters observed during whole brain analyses as well as within ROIs. This was done to explore the relationships primarily between brain response and eating disorder severity, but also to provide clues regarding developmental differences in neural functioning among those with AN.

5. Results

5.1. Demographic and Clinical Characteristics

There were no differences in age between those with AN (*Mdn*=22.00) and HC (*Mdn* =22.00, *U*=161.00, *p*=0.58). Similarly, race (*FET*=1.15, *p*=1.00), marital status (*FET*=1.87, *p*=1.00), level of education (*FET*=3.34, *p*=1.00), and occupational status (*FET*=4.86, *p*=1.00) did not significantly differ between the two groups.

As expected, Independent-sample T-test results indicated that groups differed on BMI and on other clinical measures. Specifically, BMI for the AN group (*M*=16.98, *SD*=1.35) was significantly lower than for HC (*M*=22.30, *SD*=1.31, *t*(36)=-12.29, $p<0.01$). EDE Global Scores as well as scores for each of the EDE subscales were

significantly higher for those with AN (EDE Global: *M*=3.10, *SD*=1.09, *t*(19.53)=11.15; Dietary Restraint: *Mdn*=3.20, *U*=16.00; Weight Concerns: *M*=3.66, *SD*=1.36, *t*(19.53)=10.56; Shape Concerns; *M*=3.57, *SD*=1.48, *t*(20.01)=8.95; Eating Concerns; *Mdn*=2.40, *U*=15.50, all $p<0.001$) than for HC (EDE Global: *M*=0.25, *SD*=0.22; Dietary Restraint: *Mdn*=0.00; Weight Concerns: *M*=0.28, *SD*=0.26; Shape Concerns; *M*=0.43, *SD*=0.35; Eating Concerns; *Mdn*=0.00). The AN group reported median BDI scores (*Mdn*=15.00) reflective of mild depression (Beck et al., 1996), which were significantly higher than those observed in healthy controls (BDI: *Mdn*=0.00, *U*=3.00, $p<0.001$). Participants with AN also had greater self-reported scores on the STAI (*M*=59.22, *SD*=12.58, *t*(23.05)=9.25, $p<0.001$), SSAI (*Mdn*=53.50, *U*=0.50, $p<0.001$), and TAS (*M*=68.71, *SD*=16.78, *t*(18.93)=2.77 $p<0.05$) compared to HC (STAI: *M*=29.37, *SD*=5.53, SSAI: *Mdn*=24.00, TAS: *M*=54.87.57, *SD*=8.47). See tables 1 and 2 for demographic and clinical data.

5.2. Whole-Brain Imaging Results

Whole brain analyses first examined the four comparisons between task stimuli (fear > fixation, happy > fixation, fear > happy, happy > fear) separately for both the HC and AN groups to ensure that the task activated the expected brain regions. These results are described first followed by analyses examining between group differences in activation for the fear > happy contrast (primary contrast of interest).

5.2.1. Within Group Analyses: A Check of the Model.

BOLD response to the fear>fixation and the happy>fixation conditions yielded significant clusters covering areas of the occipital cortex, bilateral temporal occipital fusiform cortex, bilateral amygdala, precentral gyrus, and left middle frontal gyrus in

both AN and HC participants. In the AN sample, additional regions of activation included the bilateral superior frontal gyrus. These two contrasts compare brain activity in response to complex facial stimuli to that of simple, neutral, non-face stimuli; therefore, activation specifically in the occipital and fusiform cortices would be expected given their role in visual face perception, recognition, and processing (Haxby, Hoffman, & Gobbini, 2000; Kanwisher & Yovel, 2006).

Amygdala activity was expected for the fear > happy contrast, but did not survive thresholding at the z=2.32, p<0.05 level; however, amygdalar activity was observed at the z=1.96, p<0.05 threshold for both groups. In AN, additional areas of BOLD response to the fear > happy contrast included the right hippocampus, left supramarginal gyrus, bilateral occipital cortices, and bilateral middle temporal gyri. In HC, additional significant clusters for this contrast included the right occipital fusiform gyrus, left temporal fusiform cortex, left middle temporal gyrus, left parahioopcampal gyrus, and left frontal cortex.

BOLD response to happy > fear contrasts yielded significant clusters in the right insula, right frontal pole, and left poscentral gyrus for the AN group. No significant clusters were observed for this contrast within the HC group. Anatomical locations of peak activation for each significant cluster observed among all four conditions in HC and AN individually are presented in table 3.

5.2.2. Between Group Analyses: Full Sample

The fear > happy contrast was the primary contrast of interest for this study (examining areas of the brain where activity to fearful stimuli exceeded that of happy emotional stimuli); therefore, only the findings for this contrast *between* HC and AN are

reported. Between group comparisons showed that the AN group had significantly lower brain activity than controls in the right and left ventral prefrontal cortex [peak voxels: (x=32, y=60, z=-8), 917 voxels, $p<0.001$; (x=-26, y=56, z=0), 719 voxels, $p<0.005$] and left lateral occipital cortex [peak voxel: (x=-34, y=-60, z=38), 541 voxels, $p<0.01$]. These findings are illustrated in figure 1.

5.2.3. Between Group Analyses with Covariates

Depression, anxiety, and low body weight are factors that have all been shown to influence brain structure and function (Friederich et al., 2012; Hall et al., 2014; Hattingh et al., 2013; Killgore & Yurgelun-Todd, 2005; Stein et al., 2007). To control for the influence of these variables, covariates were added to whole brain, between-group analyses. When including BMI as a covariate, significantly reduced ventral-medial prefrontal cortical activity was observed in the AN group compared to controls [peak voxel: (x=8, y=62, z=-16), 1530 voxels, z=1.96; cluster significance = $p<0.001$, corrected]. Location of peak voxels changed (e.g., became more medial) when adding covariates to the model; however, there was notable overlap of significant clusters observed in uncorrected and covaried analyses in both hemispheres, indicating that findings of lower activity in the ventral prefrontal cortex held when controlling for BMI. An additional finding was observed in this analysis that had not been observed in the analysis without covariates, namely reduced activity in the pregenual anterior cingulate in AN compared to controls [(x=-8, y=30, z=14), z=1.96; cluster significance = $p<0.001$, corrected]. When STAI and BDI scores were covaried, the results from the main group analyses did not withstand multiple comparison correction; however, when examined without the multiple comparison correction, ventral-medial prefrontal and pregenual

cingulate group differences were observed (z=2.30, uncorrected). Whole brain group differences, with covariates, are presented in figure 2.

5.2.4. Between Group Analyses: Unmedicated and Medicated AN vs. HC

Just over half of the AN sample (*n*=10) were taking psychotropic medications at the time of the study. To test whether the group differences noted above were driven by medication influences, whole brain group analyses were conducted comparing the nine unmedicated and ten medicated patients separately versus controls.

Visual inspection of the fear > happy contrast data showed areas of lower brain activity in ventral prefrontal regions in both the unmedicated and medicated AN subgroups compared to HCs; however, group differences did not survive multiple comparison correction.

5.3. Region of Interest (ROI) Results

Between group differences in brain response within bilateral amygdala, insula, pregenual anterior cingulate (ACC), and subgenual ACC were investigated. See figure 3 for ROI findings. When controlling for BMI, functional activity in the right pregenual ACC was significantly lower in AN for the fear > happy contrast compared to healthy controls [$F(1,34)=6.23$, $p=0.01$]. Left pregenual ACC activity was also lower in the AN group at trend levels [$F(1,34)=2.64$, $p=0.11$]. This remained the case when also controlling for self-reported STAI and BDI scores [right pregenual ACC, $F(1,34)=4.81$, $p=0.03$; left pregenual ACC, $F(1,34)=2.96$, $p=0.09$]. Effect size, measured by partial eta squared (η^2), was 0.13 and 0.09 for the right and left pregenual ACC respectively. These estimates are reflective of large effect size differences in the right pregenual ACC and medium effect size differences in the left pregenual ACC (Cohen, 1969; Richardson,

2011). Group differences were not observed when examining other regions of interest (i.e., amygdala, insula, subgenual ACC).

5.3.1. ROI results: Unmedicated and Medicated AN vs. HC

When controlling for BMI, STAI, and BDI, differences in right pregenual ACC [$F(1,20)=3.01$, $p=0.09$] and left pregenual ACC [$F(1,20)=2.70$, $p=0.11$] activity remained at trend levels between the unmedicated subsample of ANs compared to controls. Trend differences were similarly observed in right (but not left) pregenual ACC [$F(1,22)=2.79$, $p=0.10$] when examining the subset of medicated individuals with AN compared to HC.

5.4. Correlational Analyses

Within the AN patient group specifically, Pearson correlations investigated the relationship between BOLD response (mean z-scores from fear > happy contrast in ROIs and prefrontal clusters from the main whole-brain group analysis that survived thresholding) and clinical data (i.e., duration of illness, BMI, and scores from self-report measures, with EDE scores being of primary interest). To further explore the role of developmental differences in eating disorder symptoms and brain activity, correlations between age, eating disorder self-report scores, and BOLD response were also examined.

5.4.1. BOLD Response & Clinical Data in AN

The left hemisphere ventral prefrontal cluster was negatively correlated (at trend levels) with the EDE Global Score ($r(19)=-0.40$, $p=0.08$), EDE Shape Concern subscale ($r(19)=-0.40$, $p=0.08$), BDI ($r(18)=-0.44$, $p=0.06$), and the STAI ($r(18)=-0.43$, $p=0.07$). Specifically, greater severity of eating disorder, depression, and anxiety symptoms were associated with lower activation in this region (see table 4).

Brain activity within the left insula was positively correlated with the Weight Concern subscale of the EDE ($r(19)=0.45$, $p=0.05$). Activity in this region was also associated with EDE Global Score (r (19)=0.40, $p=0.09$), duration of illness (r (19)= 0.45, $p=0.53$), and trait anxiety ($r(18)=0.43$, $p=0.07$), at trend levels. BOLD response within the left subgenual ACC significantly correlated with BDI scores ($r(18)= 0.48$, $p=0.04$) and showed a negative trend with Eating Concerns (r (19)=-0.40, $p=0.08$). Right pregenual ACC activity was positively associated with duration of illness ($r(19)= 0.50$, $p=0.02$). There were no significant correlations observed between clinical data and bilateral amygdala, left pregenual ACC, right insula, or right subgenual ACC activity (see table 5).

5.4.2. Developmental Findings: Correlations with Age

Few significant correlations were observed between age and other variables. Age was not associated with any of the self-report measures of depression, anxiety, alexithymia, or eating disorder pathology. In regards to BOLD response, only activity within the left insula was positively correlated with age ($r(19)=0.50$, $p=0.02$). There were no observed relationships between brain activity in other clusters/ROIs and age (table 6).

6. Discussion

AN is a serious, often chronic mental illness with limited treatment options, due in part to an incomplete understanding of neurobiological factors underlying the illness and its persistence. Research indicates a strong genetic component to AN that is thought to influence the expression of genes that control neural systems central in emotional processing. It is hypothesized that deficits in emotion processing (e.g., emotional recognition), which have been observed in behavioral research, contribute to the

development and perpetuation of AN symptoms (Fairburn, 2003; Harrison et al., 2009; Jansch et al., 2009; Joos et al., 2009) where eating disorder behavior in AN (e.g., food restriction) may persist as a means of reducing or numbing trait-related emotional hypersensitivity (Hatch et al., 2010). Therefore, as highlighted throughout this paper, neuroimaging research investigating neural correlates of basic emotion processing in this disorder is critically important.

The purpose of the current study was to expand on the behavioral literature and on previous neuroimaging findings in eating disorders by increasing our understanding of the neurobiological underpinnings of emotional processing deficits in acute AN, focusing on innate emotional cues. Specifically, this study sought to characterize brain activity within neural circuits central to emotion processing in response to facial expressions of fear and happiness among adolescents and adults ill with AN compared to healthy controls. This study also aimed to characterize the relationship between neural activity and eating disorder symptoms. Based on study hypotheses, it was expected that individuals with AN would exhibit hyperactivity in the amygdala as well as insular and anterior cingulate regions in response to fearful facial stimuli, which would be associated with severity of self-reported eating disorder behavior.

6.1. Review of Study Findings

Independent, within group analyses indicated that the task, which has been widely used in other areas of neuroimaging research, was valid and activated relevant areas of the brain. However, contrary to expectations, hyperactivity in fronto-limbic brain regions (i.e., amygdala, insula, cingulate) was not observed between individuals with AN and healthy controls in response to fearful emotional cues. Instead, whole brain analyses

showed that, when controlling for concurrent anxiety, depression, and BMI, individuals with AN had reduced functional activity in areas of the ventral-medial prefrontal and pregenual anterior cingulate cortices when viewing fearful faces. Region of interest analyses increased confidence specifically in pregenual cingulate findings, showing that individuals with AN had significantly reduced activity in this region, which was not a consequence of psychiatric comorbidity or low weight status.

Numerous structural and functional imaging studies have implicated alterations in ventral prefrontal and cingulate cortices in AN, although the nature of the disturbance differs based on the type of imaging methodology employed. For instance, although cerebral tissue atrophies during periods of severe malnutrition, voxel-based morphometry methods have shown that those with eating disorder histories continue to show a 5% decrease in gray matter volumes within bilateral pregenual anterior cingulate cortices following recovery from AN (Muhlau et al., 2007). In a similar study, both acutely ill and long-term recovered AN (defined as individuals with BMI>17.5 kg/m^2 with both regular eating patterns and consistent menstrual cycles for 1+ years) showed decreased grey matter volumes in the anterior cingulate cortex compared to controls (Friederich et al., 2012).

Decreased blood profusion measured with SPECT technology in bilateral anterior cingulate cortices, including pregenual regions, has been shown to differentiate individuals ill with restricting AN from those with binge/purge symptoms and from healthy controls (Naruo et al., 2001), meaning that reduced ACC activity might be a biomarker specific to the restricting subtype of the illness. Takano et al. (2001) similarly reported the presence of hypoperfusion within the pregenual ACC in individuals with

acute AN compared to HC, but noted additional findings of hyperperfusion in areas of the medial prefrontal cortex, thalamus, and amygdala. Although some studies suggest that differences in blood profusion in the brain are specific to acute phases of AN (Frank et al., 2007), others have found that abnormalities persist in recovered AN groups as well (Kojima et al., 2005; Rastam et al., 2001).

Neurochemical differences assessed using magnetic resonance spectroscopy have been reported between individuals with AN and controls, where patient groups show reduced concentrations of glutamate and glutamine in the ACC (Ohrmann et al., 2004) and reduced N-acetyl-aspartate (NAA), glutamate, and myo-inositol in the middle prefrontal cortex (Castro-Fornieles et al., 2007).

As briefly described in the review above, aberrations within cingulate and ventral prefrontal brain region have similarly been observed with the use of task-based functional MRI methods that display stimuli consisting of food and body shape images. In contrast to findings from the current study and from perfusion SPECT studies, research using disease-specific stimuli tends to elicit increased brain activity in cingulate and middle frontal brain areas among those with AN (Zhu et al., 2012). For example, in order to examine the neural correlates of "calorie fear", Ellison et al. (1998) compared brain activity in six females with acute AN and six healthy controls undergoing fMRI who were presented with alternating images of high caloric drinks (i.e., chocolate milkshakes) and low calorie drinks (i.e., mineral water). In response to high calorie images, which were rated as more anxiety-provoking by the patient group, individuals with AN showed greater brain activity in the anterior cinguate gyrus as well as greater activity within the left insula and amygdala than did healthy controls. Uher et al. (2004) found that increased

brain activity in anterior cingulate and left medial orbitofrontal cortices in response to food images (e.g., pizza, cake) was common between women with both anorexia and bulimia nervosa compared to healthy comparison groups, although findings were most pronounced for unmedicated restricting type AN without concurrent depression. Individuals having recovered from restricting-type AN (i.e., stable weight above 85% ideal body weight for at least 2 years, regular menstrual cycles, no psychotropic medication) have also demonstrated increased anterior cingulate and middle prefrontal activation compared to controls when viewing food stimuli using the same task as well as increased activity in the right lateral prefrontal and dorsal anterior cingulate cortex compared to chronically ill AN groups (Uher et al., 2003).

In regards to studies examining neural components of body image dissatisfaction, individuals with AN demonstrate altered activity in pregenual anterior cingulate regions in response to human figures (i.e., slim idealized female bodies) compared to healthy controls (Friederich et al., 2010). Greater middle frontal brain response has been reported in AN groups when presented with images of others' bodies, although a general hypoactivation has been observed when individuals with AN view images of their own bodies (Sachdev, Mondraty, Wen, & Gulliford, 2008). Miyake et al. (2010) have noted that brain response to distorted self-images differentiates AN subtypes, where individuals with binge/purge symptoms demonstrate increased prefrontal activity in response to morphed images of themselves, which is not observed in restricting-type AN.

Taken together numerous investigations employing neuroimaging technology have implicated the anterior cingulate and prefrontal cortices as disturbed in AN, suggesting that these regions may be particularly important to the pathophysiology of the

illness; however, the nature of the disruption depends on the methods used. Structural neuroimaging studies suggest that gray matter loss in the anterior cingulate is present in acute AN and is not solely state-dependent. SPECT and neurochemical studies provide additional evidence that functioning within pregenual anterior cingulate and middle prefrontal regions is altered among individuals with AN, which may be especially true for the restricting subtype. Whereas hypoactivity is observed in frontal and cingulate regions with non-task based studies (e.g., SPECT, spectroscopy), task-based fMRI studies, in general, tend to show greater brain activity in these regions when using disease-specific stimuli. However, these studies do not provide any clues as to how neurobiological systems in AN function in response to basic emotional cues. Only the current study and that conducted by Cowdrey et al. (2012) have looked at brain response to basic emotional facial cues in AN in attempts to shed light on this issue.

In the study by Cowdrey et al. (2012), brain activity in response to happy and fearful faces was examined in individuals who had recovered from AN compared to healthy control participants. The task employed closely resembled that used in the present study. Participants passively viewed different facial expressions while undergoing fMRI while performing a gender discrimination task to help ensure attentive engagement. When examining brain activation to the fear > happy contrast, no differences were observed between the groups for whole brain or region of interest analyses (i.e., amygdala, fusiform gyrus). The authors concluded that impairments in emotional face processing are not present in AN after symptom remission. When considered alongside findings from the current study, which shows decreased activation in response to fearful cues, it appears that basic emotion processing at the neurobiological level may differ

depending on the phase of the illness. It is possible that alterations in cingulate and frontal activity that are present during acute AN normalize when individuals are no longer suffering from the medical and psychological consequences of the illness.

6.2. Models of Emotional Functioning

Emotional experiences are highly complex phenomena that involve changes in physiological arousal, appraisal and evaluation, subjective experience, expression, and coordination of goal-directed behavior (Phillips, Drevets, Rauch, & Lane, 2003). Regulation of these different aspects involves the interaction between numerous brain regions that collectively influence neurobiological processing of emotions. Several similar models of emotional processing, which are based on extensive animal and human research, have been put forth to help us conceptualize the biological basis of normal and abnormal emotional experiences.

As previously noted, Mayberg's (1997) Limbic-Cortical Dysregulation Model, which has been specifically applied to depressive symptomology, organizes fronto-limbic brain structures into three separate, but interconnected functional systems that collectively respond to and control emotional experiences. Specifically, Mayberg (1997) suggests that neocortical brain structures (i.e., dorsal-lateral prefrontal cortex, inferior parietal cortex, and dorsal and posterior cingulate cortex) play a regulatory role in emotion processing whereas paralimbic structures (i.e., medial orbital frontal cortex, subgenual cingulate cortex, hypothalamus, insular cortex, and amygdala) are responsible for more rapidly reacting to the salience of emotional stimuli. In addition, Mayberg notes that subcortical brain structures, specifically the pregenual cingulate cortex as well as the

striatum and thalamus, are responsible for facilitating communication *between* areas of the neocortex and paralimbic system (Mayberg, 1997; Mayberg, 2003).

A similar model explains emotion perception as a result of functioning within a ventral, affective neural system, and a dorsal, cognitive neural system (Phillips, Drevets, Rauch, & Lane, 2003). According to this model, the ventral system (comprised of the amygdala, insula, ventral striatum, subgenual and pregenual anterior cingulate cortices, and ventral-lateral prefrontal cortex) is responsible for rapidly determining the significance of an emotional stimulus, producing both conscious and unconscious affective states, and reflexively mediating responses to emotional stimuli. The dorsal component of this model (comprised of the hippocampus, dorsal anterior cingulate, and dorsal prefrontal cortex) is responsible for more effortful control of affective states and behavioral responses. According to Phillips et al. (2003), the pattern of abnormalities that exist within ventral and/or dorsal neural systems result in symptoms observed in various psychiatric disorders. For instance, authors purport that the combination of reduced volumes and decreased activity in amygdala and insular regions in conjunction with impairments in dorsal prefrontal cortical function during executive functioning tasks in Schizophrenia lead to the restriction of emotion (i.e., emotional blunting) as well as misinterpretations of social cues that contribute to persecutory delusions in the illness (Phillips, Drevets, Rauch, & Lane, 2003). Similarly, authors suggest that structural enlargements in amygdalar/caudate regions, increased resting state activity in right hemispheric temporal and subgenual cingulate regions along with decreased dorsomedial prefrontal activity leads to heightened sensitivity to emotional stimuli and difficulties

with behavioral/emotional control characteristic of mood lability in bipolar disorder (Phillips, Drevets, Rauch, & Lane, 2003).

When considered within the wider literature, findings from the present study may suggest that, whereas individuals with acute AN are oversensitive to food or body-related stimuli which tend to elicit hyperactivity in paralimbic/ventral neural systems, basic emotional cues (i.e., fearful facial expressions) inadequately trigger activity within brain structures that are responsible for ones' ability to identify affective states and automatically regulate communication between lower and higher-order brain regions.

More specifically, altered brain activity in the pregenual ACC region may contribute to the high rates of alexithymia observed in AN as well as to deficits observed in behavioral research studies examining basic emotional awareness (Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007; Bydlowski et al., 2005; Cochrane et al., 1993; Corcos et al., 2000; Eizaguirre et al., 2004; Schmidt et al., 1993; Subic-Wrana et al., 2005; Taylor et al., 1996; Zonnevijlle-Bender et al., 2002; Zonnevylle-Bender et al., 2004). As noted above, the anterior cingulate plays a major role in determining the conscious and unconscious awareness of emotions (Phan et al., 2002; Phillips, Drevets, Rauch, & Lane, 2003). Lesion studies have suggested that damage to pregenual anterior cingulate cortex is associated with emotional blunting and apathy (MacLean & Newman, 1988). The idea that alterations in the cingulate may be influencing emotional awareness in AN is consistent with research in healthy individuals that shows emotional identification as well as levels of alexithymia are inversely associated with brain activity in anterior cingulate regions in response to emotional facial stimuli (Jongen et al., 2014).

In addition, although regulation of affect and behavior can be conscious and planful, requiring the recruitment from the dorsal/neocortical systems (Phillips, Drevets, Rauch, & Lane, 2003; Mayberg, 1997), part of emotional regulation occurs automatically, outside of our conscious knowledge. In healthy individuals, pregenual anterior cingulate and ventral prefrontal structures reactively inhibit activity within amygdalar and insular regions. Specifically, anterior cingulate and ventral prefrontal structures restrain stress responses through direct anatomical connections to limbic structures (Kaufman, Plotsky, Nemeroff, & Charney, 2000). Therefore, it is possible that paralimbic responses (e.g., amygdala) to basic emotional cues are similar between AN and healthy individuals, but that those ill with AN struggle to automatically "turn off" or appropriately regulate their response to basic affective information. Deficits in unconscious emotional control secondary to functional aberrations in pregenual cingulate and ventral prefrontal regions may, in part, explain self-reported difficulties with emotional control/regulation consistently reported in AN within the literature (Brockmeyer et al., 2012; Gilboa-Schechtman et al., 2006; Harrison et al., 2009; Manuel et al., 2013; Manuel et al., 2013; Merwin et al., 2013). Of note, self-reported emotion regulation difficulties have been repeatedly shown to differ between acute AN groups and controls, but not between recovered AN and comparison samples (Harrison, Tchanturia et al., 2010). Given that Cowdrey et al. (2012) failed to find reduced activity in cingulate and frontal regions among recovered AN groups in response to fearful stimuli, this may lend further support to the idea that abnormal functioning in these areas is specific to the ill phase of the illness.

6.3. Social Implications of Abnormal Processing in Emotional Brain Circuits

The Social-Emotional Processing Stream, a translational model adopted by Oschner (2008) and later adapted for use in AN specifically (Oldershaw et al., 2011), suggests that emotional behavior and social information processing share underlying brain systems and are thus inextricably linked (Olsson & Ochsner, 2008). Oschner (2008) notes that, although it is possible for non-social stimuli to elicit emotion (e.g. feeling disgust in response to garbage), it is difficult to engage in social interactions completely bereft of emotion. Although this paper is focused on emotional behavior in AN, the consideration of related social-emotional processes may be particularly appropriate for this disorder given that, in addition to emotional abnormalities, difficulties with social functioning are thought to play an important role in the illness. Individuals with AN have avoidant and insecure attachments styles (Ward et al., 2001), limited social networks, and are typically shy and submissive (Fairburn, Cooper, Doll, & Welch, 1999; Tiller et al., 1997). Social phobia predates AN onset in a majority of cases and is found in 55% of those with current AN (Harrison et al., 2010). Additionally, interpersonal stress is one of the most common precipitating stressors prior to AN onset (Schmidt, Tiller, Blanchard, Andrews, & Treasure, 1997; Schmidt & Treasure, 2006).

Aspects of social cognition, specifically the ability to recognize and represent the emotional experience of others is regulated, in part, by the ventral medial prefrontal cortex (Jenkins et al., 2014; Vandekerckhove et al., 2014), an area identified in the current study as hypoactive in AN. For example, individuals with lesions within ventral medial prefrontal regions perform significantly worse on facial emotion recognition tasks, especially for fear (Jenkins et al., 2014). Hypoperfusion in this region using SPECT has also been linked to poor recognition of facial expressions (i.e., fear, disgust,

and surprise) and is associated with impairments in empathy (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Vandekerckhove et al., 2014). Given this information, it is possible that decreased activation in ventral medial prefrontal regions in response to fearful cues in AN helps explain deficits in emotion recognition observed in numerous behavioral studies (Kucharska-Pietura et al., 2004; Pollatos et al., 2008) and also contributes to social impairments in this disorder.

6.4. Relationships Between Brain Response, Demographics, and Behavioral Measures

As previously noted, several investigators have speculated that eating disorder behaviors in AN are maladaptive means of coping and are negatively reinforced due to their attenuating effect on difficult emotional experiences (Engel et al., 2013; Merwin et al., 2013; Smyth et al., 2007). In this study, it was therefore hypothesized that eating disorder symptoms, specifically dietary restraint, a hallmark characteristic of anorexia nervosa, would be associated with brain response to fearful faces. Although correlational analyses are not able to provide information about direction of effect or causation, they would yield indirect evidence that emotion processing abnormalities may be related to eating disorder behavior and their maintenance in AN.

Contrary to expectations, amygdala activity in the AN group was not associated with dietary restriction or other measures of eating disorder psychopathology, suggesting that an underlying emotional hypersensitivity to basic emotion stimuli is not directly perpetuating AN behavior. Trends suggested that functional activity within the right ventral prefrontal cortex was associated with overall eating disorder severity; however, reduced prefrontal brain activity was also linked to symptoms of depression and anxiety

suggesting that activation in prefrontal regions may not be so much involved in perpetuation of eating disorder symptoms in AN so much as a marker of general psychopathology or illness severity. Response within insular regions specifically, and to a lesser degree that within pregenual cingulate regions, may also be markers of illness severity given relationships with duration of illness and EDE Global Scores. Greater activity within the subgenual anterior cingulate was positively associated with depression severity, which is consistent with previous findings implicating this region as being particularly important in depressive symptomology (Connolly et al., 2013; Drevets, Drevets, Savitz, & Trimble, 2008; Gotlib et al., 2005; Keedwell et al., 2010; Mayberg, 1997; Merkl et al., 2009; Siegle et al., 2012). Additionally, age was significantly correlated with left insular activity in response to fearful faces, suggesting that function in this brain region may change over the course of development in those with AN. Significant brain changes, such as synaptic pruning and reorganization, occur as individuals mature from adolescence into young adulthood (Lenroot & Giedd, 2006; Romeo & McEwen, 2006) that include marked structural and functional changes within fronto-limbic brain regions such as the anterior insula (Blakemore, 2008). Studies examining larger adolescent AN samples are needed to further replicate these findings and further examine why other regions (e.g., medial prefrontal cortex) were not associated with developmental changes in this population.

Although findings suggest that dietary restriction is not directly associated with activity within fronto-limbic brain regions, there are other possible explanations for the lack of observed relationships. In this study, dietary restriction was measured using the restraint subscale of the EDE. This subscale quantifies the frequency (i.e., number of

days) with which an individual has wanted to and/or actually engaged in restrictive eating behavior over the past month. Therefore, it yields a measure of the overall severity of cognitive and behavioral aspects of dietary restraint over the course of several weeks. With task-based fMRI, we are measuring momentary changes in brain response to brief stimuli. It is possible that real-time changes in neurobiological functioning are associated with momentary changes in thoughts or efforts to restrict in AN, but that the temporal characteristics of the EDE (i.e., a retrospective instrument) do not capture this relationship. Assessing momentary aspects of eating disorder behavior concurrently with fMRI scanning may be able to shed light on this issue in the future.

Relationships between self-reported alexithymia (i.e., TAS-26) and brain response were not observed, which was surprising given previous research suggesting the contrary (Berthoz et al., 2002). However, the TAS-26 was only collected on a subset of those with AN in this study, so it is possible that there was not enough power in this smaller sample to detect meaningful relationships between alexithymia and fronto-limbic brain activity.

6.5. A Discussion on the Absence of Amygdala Findings

This study specifically hypothesized about activity within the amygdala as this brain region directly responds to fear (Augustine, 1996; Ongur & Price, 2000; Fusar-Poli et al., 2009; Sheline et al., 2001), because fear has been considered especially important within the context of AN, and on account of previous neuroimaging findings that have implicated altered amygdala activity in the pathophysiology of the illness. However, unlike previous neuroimaging studiess in eating disorders, this study did not observe group differences in amygdala response between AN and healthy controls. The lack of hypothesized amygdala hyperactivity to fearful faces in AN may be due to several

reasons. There may be unique differences in the way that emotional-laden, disease-specific cues (i.e., images of body shapes or high caloric food) are processed in AN compared to basic interpersonally-based emotional stimuli (i.e., emotional faces). As previously mentioned, it is possible that the initial response to general cues of fear or threat is not disturbed in AN, but that subsequent automatic regulation of emotion is disrupted. Additionally, heighten amygdala activity observed in previous studies might be reflective of conditioned fear responses (Morris et al., 1998) and increased attention/vigilance (Gallagher, Graham, & Holland, 1990) specifically to food and body-related information in the illness.

In addition, happy faces were chosen as a comparison condition in this study in order to avoid problems associated with processing biases of neutral, more ambiguous emotional stimuli (i.e., neutral faces, Maniglio et al., 2014) and because it allowed for more direct comparison with the only other neuroimaging study to date that has specifically investigated brain activity in response to basic emotional cues in eating disorders (Cowdrey et al., 2012). Although the amygdala is more sensitive to fearful emotional faces (Fusar-Poli et al., 2009), studies have also noted that happy expressions elicit amygdala activity (Fusar-Poli et al., 2009; Suslow et al., 2010; Victor et al., 2012). It is possible that there were limited observable effects on account of diminished contrast between the two emotional stimuli used in this study.

Lastly, others have argued that other emotions, aside from fear, might be important to consider in AN. For example, behavioral studies have found that individuals with AN have deficits in regards to processing emotions of surprise (Kessler et al., 2006) and sadness (Kucharska-Pietura et al., 2004; Pollatos et al., 2008). In addition, significant

evidence exists suggesting abnormalities in anger and disgust processing in the illness. For example, individuals ill with AN, as well as those who have recovered from the illness, demonstrate biased attention towards angry faces (Harrison, Tchanturia et al., 2010) and misclassify more facial expressions as angry (Jansch et al., 2009). In addition, those with AN report high state anger scores but tend to restrain the expression of this emotion (Geller, Cockell, Hewitt, Goldner, & Flett, 2000; Joos et al., 2011; Waller et al., 2003). In regards to disgust, individuals with AN appear to be hypersensitive to this emotion (Aharoni & Hertz, 2012), particularly in response to self-referent as well as food and body-related cues (Geller, Cockell, Hewitt, Goldner, & Flett, 2000; Harvey, Troop, Treasure, & Murphy, 2002; Troop, Murphy, Bramon, & Treasure, 2000). In unmedicated individuals, AN severity has been associated with decreased accuracy in classifying facial emotions of disgust (Jansch et al., 2009). [Of note, the anterior insula is directly related to processing the emotion of disgust (Vicario, 2013; Wicker et al., 2003; Woolley et al., 2015). The lack of disgust-eliciting stimuli in the present study may explain why insular findings were not observed].

Fox and Power (2009) have developed an emotions-based model of eating disorder development and perpetuation that highlights anger and disgust as of primary importance to AN. In this model, external and internal events (e.g., interpersonal interactions, sensory experiences, visual images, automatic thoughts/verbal statements) trigger schemas that involve the self being viewed as being bad/worthless, others as being hurtful and more important, and the world as being harmful and unfair. These schemas prime individuals to experience anger. However, authors suggest that individuals with eating disorders learn over time to associate anger as being ‘bad’ or ‘wrong’ leading to

suppression of this emotion. Disgust, which is directed towards the self and towards food, then gets coupled with and functions to suppress the experience of anger. Disgust and fear are related, in that they are both emotions of avoidance (Uher et al., 2005); however, according to the model put forth by Fox and Power (2009), fear observed in AN, specifically fear of food and weight gain, is not primary, but develops secondary to the presence of disgust. This model would suggest that stimuli aimed at eliciting fear responses may not be the ideal stimuli to investigate neurobiological underpinnings of emotional problems in AN. Neuroimaging studies using anger-inducing or disgust-inducing stimuli may be more likely to differentiate individuals with AN from HC than those specific to fear.

6.6. Study Strengths and Limitations

This study had a number of strengths. Sample size included in the present study was large in comparison to most other neuroimaging studies investigating brain activity in eating disorder populations. It is the first study to examine neurobiological underpinnings of basic emotional processing during acute phases of the illness in both adolescents and adults, which is a significant gap in the eating disorder literature. In addition, scanning parameters employed a multi-band sequence, which increases spatial resolution of acquired images and increases the ability to detect differences in brain response.

Despite study strengths, there are a number of limitations to note. The study was powered to detect large effects, so it is unknown whether small or medium effects were present between AN and HC groups in regards to amygdala and other ROI activity. Although follow-up analyses attempted to examine whether psychotropic medication use

influenced study findings, the lack of differences between both medicated and unmedicated AN versus controls likely points to low power among these subsequent comparisons. In addition, the study was cross-sectional in nature, which limits direct conclusions that can be drawn about disease maintenance. Healthy controls were free from lifetime eating disorder symptoms, but were not required to report an absence of other mental health conditions, which could have impacted findings. Only females with the restricting subtype of AN were included in this study which limits the generalizability of findings to males and those with binging and purging symptoms. As previously mentioned, AN typically develops during adolescents (Golden, 2003) when neural pruning and refinement takes place (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000). Younger age of onset has been shown to predict outcome in AN (Fisher, 2003; Herpertz-Dahlmann et al., 2001). Although the current study included adolescents and examined the relationships between age, eating disorder symptoms, and brain response, the sample was too small to fully investigate developmental differences.

In addition, this study looked specifically at brain activity in response to two basic emotions (i.e., fear, happy); however, the paradigm did allow for the examination of other basic emotions (i.e., anger, disgust, sadness), which as previously described, may be particularly important to AN physiology.

Instruments assessing eating disorder behavior were retrospective in nature and did not allow for investigation of the real-time relationships between brain response and dietary restriction in AN. In addition, the study did not include a self-report measure of emotional regulation. Findings from this study suggest that individuals with AN may have deficits in the automatic control of emotional reactions; thus, it would have been

helpful to be able to relate neurobiological findings directly to behavioral measures of emotional regulation to increase confidence in this conclusion. Additionally, including a non- passive viewing task (e.g., one that examines differences in emotion recognition abilities) in conjunction with fMRI data acquisition would have added to the value of this study.

Although BMI was covaried during analyses to control for severity of low-weight status, the ill phase of the illness is associated with other metabolic, electrolyte and endocrine disturbance which may influence brain function (Frank & Kaye, 2012). The inclusion of a recovered group in addition to those ill with AN could have improved the study design and allowed for further control of these issues. The alexithymia measure was only collected on a subset of the sample; therefore alexithymia was not considered as a covariate in imaging analyses. This would have been a helpful addition given that rates of alexithymia are particularly elevated in eating disorder populations (Berthoz, Perdereau, Godart, Corcos, & Haviland, 2007; Cochrane et al., 1993; Corcos et al., 2000; Eizaguirre et al., 2004; Schmidt et al., 1993; Subic-Wrana et al., 2005; Taylor et al., 1996; Zonnevijlle-Bender et al., 2002; Zonnevylle-Bender et al., 2004).

Lastly, abnormalities within the anterior cingulate cortex and ventral prefrontal cortex have been observed in other types of psychopathology, such as depression and anxiety (Angelini, Mazzucchi, Picciotto, Nardocci, & Broggi, 1981; Phillips, Drevets, Rauch, & Lane, 2003a; Stuhrmann et al., 2011). Similarly, emotion processing deficits are also observed across numerous forms of mental illness and are not specific to eating disorder diagnoses (Giloba-Schechtman et al., 2006; Zonnevylle-Bender, van Goozen, Cohen-Kettenis, van Elburg et al., 2004). Although this study controlled for current levels

of self-reported depression and anxiety symptoms, the study did not fully assess and control for the presence of full co-morbid psychiatric disorders nor did it include other psychiatric comparisons groups. Therefore, it is not possible to determine whether findings from the present study are specific to AN, reflect the overlap between AN and common psychiatric comorbidities, or are reflective of deficits in emotional processing to psychopathology in general. Future research is needed to better address these study limitations.

6.7. Future Directions

Although the current study provides evidence of disturbed functioning within fronto-limbic regions in AN, specifically the pregenual ACC and ventral prefrontal cortex, Zucker et al., (2007) has noted that "the specific difficulties associated with AN and their underlying neural mechanisms are elusive and understudied". Therefore more neuroimaging studies will be important to further our understanding of neural correlates in the disorder that may be reflective of biological vulnerability to AN and its persistence.

In the future, studies should include even larger medication-free sample sizes and incorporate groups of males with AN as well as those with the binge/purge subtype. Longitudinal designs that allow for the investigation of brain response to a wide variety of different emotional stimuli among ill individuals and following successful recovery, or among those at high risk for developing AN, will be important for clarifying neurobiological aspects of disease development and maintenance. Furthering this work in adolescent and early-onset AN may be especially important in order to identify neurobiological mechanisms uncompromised by the scarring effects of chronic illness and to identify targets for early intervention.

In addition, instead of using retrospective measures, assessing more momentary aspects of dietary restraint and emotional regulation would allow for the examination of temporal relationships between neural and behavioral correlates of emotion processing deficits in AN. For instance, future neuroimaging studies could integrate ecological momentary assessment methods, which measure variables in real time, with scanning paradigms to assess thoughts and urges to restrict or manipulate food intake directly after exposure to emotionally salient stimuli.

This study looked specifically at function within specific brain regions. However, both the integrity of individual fronto-limbic structures *and* the links between them collectively control emotional processing (Mayberg, 1997). Studies that examine both functional activity in important brain regions (e.g., pregenual anterior cingulate cortex) as well as the connections with other fronto-limbic structures (e.g., with resting-state fMRI) will be important in regards to broadening our understanding of how these circuits behave in concert to control emotions in AN.

Lastly, this study examined neural responses to emotional cues between a discrete, categorical group of individuals with AN compared to those without the disorder. However, eating disorders, including AN, are heterogeneous phenotypes. To truly understand the role that emotions play in the development or maintenance of eating disorder pathology, it may be that approaches examining the relationship between brain response to narrower domains of disordered eating (e.g., restraint, eating concerns, etc.) will be more likely to yield reliable and valid neurobiological markers of psychiatric illness. This type of approach is consistent with the Research Domain Criteria (RDoC) proposed by the NIMH, which aims to move mental health research away from the

current diagnostic system, and towards a classification system based on a multi-method, dimensional approach. In other words, RDoC studies look at homogeneous symptoms that may exist across several currently defined disorders and attempts to understand these symptoms across multiple units of analysis (e.g., genetics, neurobiology, behavior). Future research could build on the current study by examining neurocircuitry of acute threat (under RDoC's negative valence domain) in individuals who engage in dietary restriction across the full eating disorder spectrum. Future studies addressing these concerns have the potential to advance our understanding of the neurobiological underpinnings of abnormal emotion processing not just among those with AN, but with those suffering from eating disorder psychopathology.

6.8. Conclusions and Implications

Anorexia Nervosa is an often devastating mental illness with a poor prognosis. Empirical studies that advance our understanding of the neurobiological underpinnings that contribute to this disorder are critically needed in order to better guide development of effective prevention and treatment strategies that reduce the personal and societal burdens of this disease. Although significant research has examined neural correlates of disease-specific cues, such as food and body-related stimuli, better understanding basic emotion circuitry in AN is especially important given that emotional problems predict poor outcome (Herpertz-Dahlmann et al. 2001; Taylor 1997) and interfere with treatment success (Speranza et al. 2007). Findings from the current study suggest that during the ill state of restricting-type AN, fearful facial expressions elicit decreased functioning in anterior cingulate and ventral prefrontal regions, areas of the brain that are central to emotional processing. Disruptions in neural activity may contribute to deficits in

emotional awareness, recognition, and automatic emotional control, which have been widely observed within behavioral studies among individuals with AN. Future research that employs momentary measures of eating disorder behavior in conjunction with emotion-based neuroimaging methods are needed to build upon findings of the current study, further elucidating our understanding of the role of neurobiological mechanisms of emotion processing deficits in eating disorders. Such studies may eventually lead to the development of biologically-based or emotion-focused treatments.

Table 1. Demographic, symptom history, and treatment history.

		AN (*N*=19)		HC (*N*=19)			
		M	***SD***	***M***	***SD***	***TS***[†]	***p***
Age (years)		22.32	3.87	22.95	3.67	161.00	0.58
BMI (kg/m^2)		16.98	1.35	22.30	1.31	-12.29	<0.01
Duration of Illness (yrs)		8.11	4.42				
		N	***%***	***N***	***%***	***TS***	***p***
Race[a]	*Caucasian*	17	89.47	17	94.44	1.15	1.00
	Hispanic	1	5.26	--	--		
	Biracial	1	5.26	1	5.56		
Relationship Status[a]	*Never married*	18	94.73	17	94.44	1.87	1.00
	Married	1	5.26	--	--		
	Divorced	--	--	--	--		
	Other[*]	--	--	1	5.56		
Education[ab] (highest level achieved)	*HS diploma*	1	5.88	--	--	3.34	1.00
	Trade school	1	5.88	--	--		
	Some college	7	41.17	7	38.88		
	College graduate	4	23.52	7	38.88		
	Graduate study	3	17.64	2	11.11		
	Graduate degree	1	5.88	2	11.11		
	Post-graduate	--	--	--	--		
Occupational Status[a]	*Full-time job*	5	26.31	3	16.66	4.86	1.00
	Part-time job	--	--	1	5.55		
	Student full-time	12	63.15	12	66.66		
	Student part-time	--	--	2	11.11		
	Unemployed	2	10.52	--	--		
		N	***%***				
Eating Disorder Behavior (Hx)	*OBE*	4	21.05				
	Vomiting	6	31.57				
	Laxative abuse	4	21.05				
	Diuretic abuse	1	5.26				
	Diet Pills	1	5.26				
Psychiatric Medications (current)	*Any*	10	52.63				
	Antidepressant	10	52.63				
	Antipsychotic	1	5.26				
	Stimulant	2	10.52				
	Tranquilizers	3	15.78				
Outpatient Tx		10	52.63				
Hospitalizations		7	36.84				

AN=Anorexia Nervosa; HC=Healthy Controls;
[†]TS=test statistic: t-statistic (BMI), Mann-Whitney U (age), Fisher's Exact Test (race, relationship status, education, occupational status); HS=High School, Tx=Treatment; Hx=self-reported history;
OBE=objective binge eating (eating large amount of food + loss of control)
[*]Cohabitating with a romantic partner
[a] Data missing from *n*=1 HC; [b] Data missing from *n*=2 AN

Table 2. Clinical data for patients with Anorexia Nervosa (AN) and Healthy Controls (HC).

	AN (*N*=19)		HC (*N*=19)		
	M	***SD***	***M***	***SD***	***TS***[†]
BDI[a]	19.00	10.74	0.78	1.39	3.00***
STAI[b]	59.22	12.58	29.37	5.53	9.25***
SSAI[b]	51.94	13.06	24.00	3.78	0.50***
TAS-26[c]	68.71	16.78	54.87	8.47	2.77*
EDE GLOBAL	3.10	1.09	0.25	0.22	11.15***
Dietary Restraint	2.97	1.48	0.18	0.44	16.00***
Weight Concerns	3.66	1.36	0.28	0.26	10.56***
Shape Concerns	3.57	1.48	0.43	0.35	8.95***
Eating Concerns	2.21	1.14	0.11	0.41	15.50***

AN=Anorexia Nervosa; HC=Healthy Controls; BDI=Beck Depression Inventory; STAI= Spielberger Trait Anxiety Inventory; SSAI= Spielberger State Anxiety Inventory; TAS-26=Toronto Alexithymia Scale; EDE Global=Eating Disorder Examination Global Score

[a] Data missing from *n*=1 AN & HC; [b] Data missing from *n*=1 AN; [c] Data missing from *n*=5 AN & *n*=4 HC

[†]TS=test statistic: t-statistic (TAS, STAI, EDE Global, Weight Concerns, Shape Concerns), Mann-Whitney U (BDI, SSAI, Dietary Restraint, Eating Concerns)

*$p<0.05$, **$p<0.01$, ***$p<0.001$

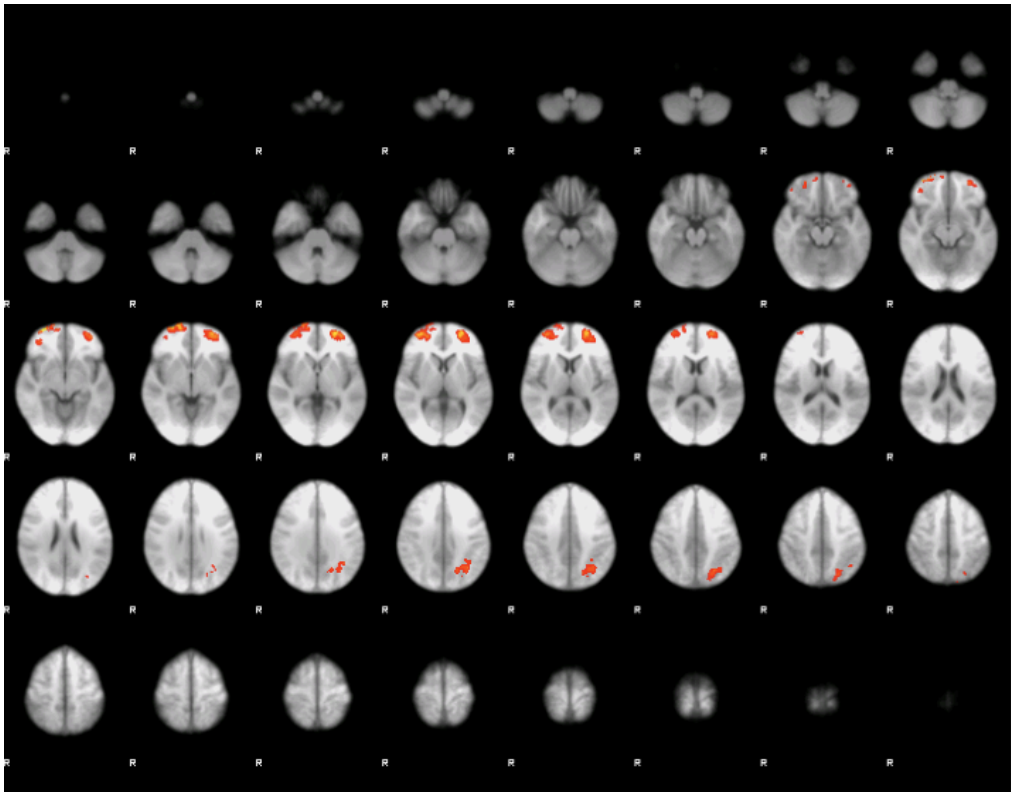
Table 3. Anatomical locations and z-scores associated with peak activation of significant clusters observed between HC (*n*=19) and the AN sample (*n*=19) with z threshold value = 2.32, $p<0.05$.

Contrast	Anatomical Location	MNI Coordinates (mm)			Z[a]	Cluster (voxels)
		X	Y	Z		
AN						
Fear > +	L occipital cortex	-12	-98	-2	6.33	33511***
	L occipital fusiform gyrus	10	-86	-18	5.96	
	R temporal occipital fusiform cortex	38	-56	-24	5.91	
	R amygdala	24	-2	-16	3.06	
	L amygdala	-24	-4	-18	3.37	
	L superior frontal gyrus/frontal pole	-10	38	50	3.73	2243***
	L inferior/middle frontal gyrus	-36	14	26	4.34	1579***
Happy > +	L occipital cortex	-12	-98	0	6.19	29257***
	R occipital fusiform gyrus	6	-84	-18	5.91	
	R temporal occipital fusiform gyrus	36	-58	-18	4.25	
	R amygdala	20	-6	-18	3.92	
	L amygdala	-18	-6	-18	3.64	
	L superior frontal gyrus	-4	42	40	4.29	2831***
	R superior frontal gyrus/frontal pole	6	54	26	4.08	
	L middle frontal gyrus	-38	14	30	4.55	2260***
	Precentral gyrus	4	-22	64	3.97	615***
Fear > Happy[†]	R middle temporal gyrus	44	-58	4	3.87	2097***
	R amygdala	22	-8	-22	2.83	
	R hippocampus	30	-12	-18	3.56	
	R lateral occipital cortex	54	-60	14	3.53	
	L lateral occipital cortex	-40	-64	8	3.65	979**
	L middle temporal gyrus	-48	-62	6	3.34	
	L supramarginal gyrus	-44	-52	18	3.23	
Happy > Fear	R insular cortex	38	-14	6	3.68	516*
	L postcentral gyrus	-50	-18	26	3.46	492*
	R frontal pole	30	60	-8	3.87	480*
HC						
Fear > +	L occipital cortex	-16	-100	12	6.41	30747***
	R occipital cortex	40	-80	14	5.98	
	R temporal occipital fusiform cortex	44	-74	16	6.20	
	R amygdala	22	-4	-18	3.01	
	L amygdala	-24	-4	-18	3.73	
	L precentral gyrus	-38	-2	48	4.26	1165***
	L middle central gyrus	-40	10	30	4.09	
	R middle frontal gyrus/precentral gyrus	44	6	44	4.28	935***
Happy > +	L temporal occipital fusiform cortex	-38	-52	-22	7.00	19157***
	R temporal occipital fusiform cortex	38	-52	-20	4.92	
	Occipital pole	0	-94	02	4.63	
Fear > Happy[†]	R occipital fusiform gyrus	10	-82	-20	3.85	10927***
	L temporal fusiform cortex	-36	-28	-26	3.76	
	R middle temporal gyrus	46	-56	14	3.55	
	L parahippocampal gyrus	-26	-22	-26	3.45	
	L amygdala	-14	-2	-12	2.05	
	L frontal pole	-22	36	-24	3.79	1093**
	L frontal orbital cortex	-28	30	-22	3.10	
Happy > Fear	--	--	--	--	--	--

[†]Findings based on z threshold value = 1.96, $p<0.05$; clusters corrected for multiple comparisons
[a]Z-score

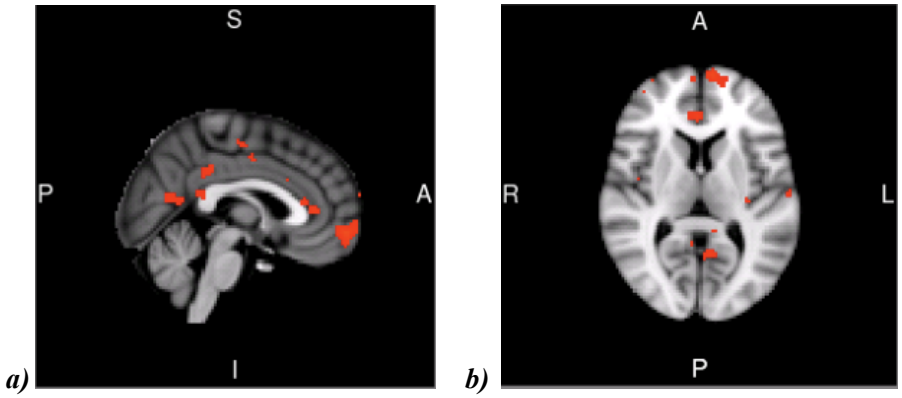
R = right hemisphere, L = left hemisphere, + = fixation cross
$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

Figure 1. Whole-brain group comparisons between patients with Anorexia Nervosa (AN) and healthy controls (HC).



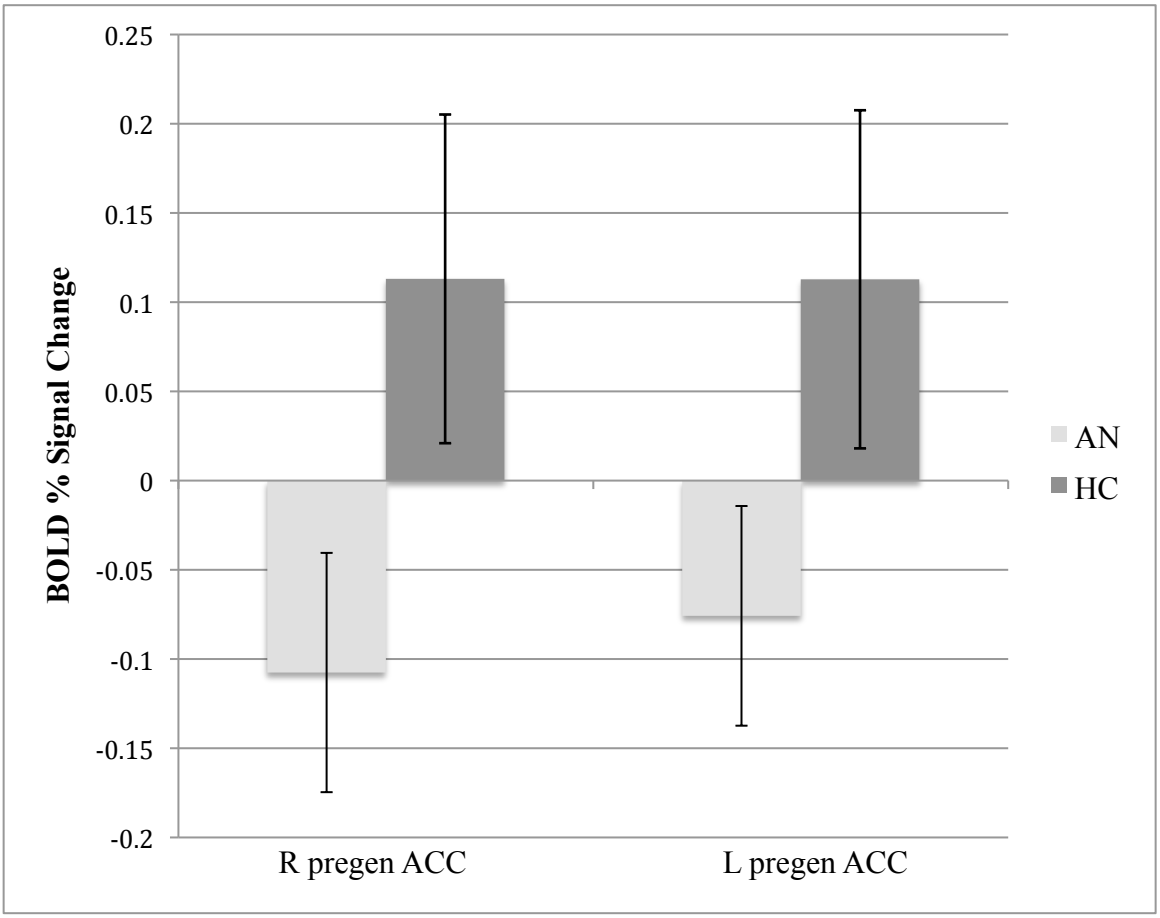
Transverse slices showing decreased activation in patients with anorexia nervosa compared to healthy controls in response to the fearful > happy contrast within 3 clusters: bilateral frontal pole [(x=32, y=60, z=-8), 917 voxels, $p<0.001$; (x=-26, y=56, z=0), 719 voxels, $p<0.005$] and left lateral occipital cortex [(x=-34, y=-60, z=38), 541 voxels, $p<0.01$]. Voxels exceeded initial threshold, z = 2.32, and survived multiple comparison correction, $p<0.05$.

Figure 2. Whole-brain group comparisons with BMI, anxiety, and depression scores covaried.



(a) Sagittal slice, and (b) axial slice depicting brain areas (i.e., ventral-medial prefrontal cortex, pregenual anterior cingulate cortex, posterior cingulate cortex, left parahippocampal gyrus) that showed decreased activation in AN participants compared to healthy controls in response to the fearful > happy contrast when controlling for body mass index, depression (BDI), and anxiety (STAI) scores. Voxels exceeded initial threshold, z = 2.32, uncorrected.

Figure 3. Between group differences in pregenual anterior cingulate activity



Between group differences in mean BOLD % signal change in the right (R) and left (L) pregenual cingulate cortex (pregen ACC) to the fear > happy contrast (bars represent standard error). Findings displayed above are conrolled for comorbid anxiety (STAI), depression (BDI) and body mass index. R pregenACC, $F(1,34)=4.81$, $p<0.05$; L pregenACC, $F(1,34)=2.96$, $p=0.09$.

Table 4. Pearson correlations between BOLD response for fear > happy contrast (whole brain clusters that survived thresholding) and clinical data in AN group

	Left Hemisphere	Right Hemisphere
	Frontal Pole Cluster	Frontal Pole Cluster
BMI	-0.06	-0.05
DOI	-0.07	-0.09
BDI	**-0.44**$^{\bullet}$	-0.05
STAI	**-0.43**$^{\bullet}$	0.05
SSAI	-0.30	-0.04
TAS-26	-0.43	0.08
EDE GLOBAL	**-0.40**$^{\bullet}$	-0.03
Dietary Restraint	-0.19	-0.07
Weight Concerns	-0.32	0.24
Shape Concerns	**-0.40**$^{\bullet}$	-0.02
Eating Concerns	-0.36	-0.29

BMI=Body Mass Index; DOI=Duration of Illness; BDI=Beck Depression Inventory; STAI= Spielberger Trait Anxiety Inventory; SSAI= Spielberger State Anxiety Inventory; TAS-26=Toronto Alexithymia Scale; EDE Global=Eating Disorder Examination Global Score

$^{*}p<0.1$, $^{**}p<0.05$

Table 5. Pearson correlations between BOLD response for fear > happy contrast (ROIs) and clinical data in AN group

	Left Hemisphere				Right Hemisphere			
	AMG	INSL	sgACC	pgACC	AMG	INSL	sgACC	pgACC
BMI	-0.16	-0.06	-0.19	-0.28	-0.07	-0.00	-0.08	-0.40
DOI	0.19	**0.45***	0.31	0.29	0.25	-0.30	0.38	**0.50****
BDI	0.33	0.29	**0.48****	0.24	0.24	0.05	0.38	0.26
STAI	0.12	**0.43***	0.15	0.15	0.19	-0.01	0.14	0.03
SSAI	0.15	0.27	0.20	0.19	0.36	0.19	0.18	0.14
TAS-26	0.39	0.25	0.44	0.41	0.21	-0.34	0.31	0.18
EDE GLOBAL	-0.17	**0.40***	-0.08	-0.03	-0.04	0.10	-0.06	-0.04
DR	-0.30	0.33	-0.11	0.08	-0.08	0.20	-0.02	0.15
WC	0.18	**0.45****	0.16	0.14	0.25	0.00	0.14	0.04
SC	-0.08	0.28	0.01	-0.07	-0.06	0.00	-0.01	-0.14
EC	0.38	0.17	**-0.40***	-0.30	-0.28	0.13	-0.35	-0.22

AMG=Amygdala; INSL=Insula; sgACC=subgenual anterior cingulate cortex; pgACC=pregenual anterior cingulate cortex; BMI=Body Mass Index; DOI=Duration of Illness; BDI=Beck Depression Inventory; STAI= Spielberger Trait Anxiety Inventory; SSAI= Spielberger State Anxiety Inventory; TAS-26=Toronto Alexithymia Scale; EDE Global=Eating Disorder Examination Global Score; DR=Dietary Restraint; WC=Weight Concerns; SC=Shape Concerns; EC=Eating Concerns

*$p<0.1$, **$p<0.05$

Table 6. Pearson correlations between age and both EDE scores and BOLD response to fear > happy contrast

	Age
Self-reported Eating Disorder Sxs (EDE)	
Dietary Restraint	0.22
Weight Concerns	0.13
Shape Concerns	0.12
Eating Concerns	0.30
Global Score	0.23
Brain (BOLD) Response	
Left Hemisphere	
Ventral PFC	-0.14
AMG	0.08
INSL	**0.50****
PregenACC	0.05
SgACC	0.19
Right Hemisphere	
Ventral PFC	-0.19
AMG	0.10
INSL	-0.27
PregenACC	0.34
SgACC	0.24

Sxs=symptoms; EDE=Eating Disorder Examination; PFC=prefrontal cortex; AMG=Amygdala; INSL=Insula; sgACC=subgenual anterior cingulate cortex; pregenACC=pregenual anterior cingulate cortex
$^{*}p<0.1$, $^{**}p<0.05$

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