Domain-General Affect: Neural Mechanisms and Clinical Implications

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

Emotions guide the way individuals interact with the world, influencing nearly every psychological process from attention, to learning, to metacognition. Constructionist models of emotion posit that emotions arise out of combinations of more general psychological ingredients. These psychological ingredients, however, also form the building blocks of other affective responses such as subjective reactions to rewarding and social stimuli. Here, I propose a domain-general account of affective functioning; I contend that subjective responses to emotional, rewarding, and social stimuli all depend on common psychological and neural mechanisms. I support this hypothesis with three independent studies using both a basic science approach and a clinical approach. In the first study (Chapter 2) I demonstrate that the ventromedial prefrontal cortex (vmPFC), which has been implicated in encoding the value of primary, monetary, and social rewards, also encodes the hedonic value of emotional stimuli. In addition to showing that the mechanisms responsible for processing affective information are shared across reward and emotional processing, I also discuss the relevance of a domain-general constructionist account of affect for clinical disorders. In particular, I hypothesize that in anorexia nervosa (AN), affective disturbances should be manifest across responses to emotional, rewarding, and social stimuli (Chapter 3). In Chapter 4, I provide empirical evidence for this conclusion by demonstrating that when viewing social stimuli, women

with a history of AN show disturbances in the insula, a brain region that is responsible for interoceptive and affective processing. This suggests that the interpersonal difficulties frequently observed in patients with AN may be due to biases in domain-general affective responses. In Chapter 5, I support this conclusion by showing that individual differences in harm avoidance in healthy women, women with a current diagnosis of AN, and women who have recovered from AN explain the relationship between disordered eating and social dysfunction. Collectively, these results indicate that subjective affective responses to rewarding, emotional, and social information all rely on common mechanisms as would be suggested by a domain-general theory of affect. Furthermore, the application of a constructionist domain-general account of affect can help to explain the fundamental nature of affective disturbances in psychiatric disorders such as AN.

Dedication

To women and girls, their bodies, and their struggles.

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Lab member. I had virtually no mathematic or statistical training. Learning to program drew demons from within me that I did not even know existed. Ask anyone. And yet, Scott was still willing to put me, a reformed art major, in his "queue," compassionately answering questions like "but what *is* a histogram?" without making me feel defeated.

Perhaps one of the best things I have learned working with Scott is how to fail. At face value this might seem negative, but in actuality, it is an invaluable skill. Before I began in Scott's lab, I generally only pursued endeavors in which I knew I would be successful. Though this certainly helped my self-esteem, it meant I was never truly challenged. Working with Scott has taught me that it is better to be challenged, fail, and try again, than to stick with something safe. With this new perspective, I have learned so much about science and feel like I could learn almost anything else. In addition gaining scientific expertise through Scott's mentorship, I have also learned what a rare and special thing it is to have a mentor who truly supports your specific goals. Scott has provided me with so much help and advice about scientific projects and presentations and also about my career. I cannot express enough gratitude for this. I am also grateful for his tolerance of what can only be described as complete nonsense (e.g., office trolls, hundreds of Dixie cups full of water, and failed cardboard box pranks).

1. Mechanisms of Domain-General Affective Processing

Emotions lie at the heart of what it means to be human. They guide our attention, transform our memory, and influence what decisions we make. Philosophical descriptions of emotion can be found in the works of Aristotle, Plato, Descartes, Hume and numerous others (de Sousa, 2014). Moreover, scientists such as William James and Carl Lange provided early conceptual models of emotion more than a hundred years ago (Cannon, 1927). Despite this rich history and the substantial progress that has been made, emotion is still relatively poorly understood, in part due to the methodological difficulties inherent in quantifying it, but also because of the difficulty of defining it.

Though definitions of emotion vary somewhat, most contend that emotion is comprised of physiological reactions, subjective feeling states, and behavioral reactions that in combination, prepare an organism to react appropriately to salient stimuli in the environment. Further, emotions involve appraisals both before and during the experience of a feeling state (Izard, 2010). This definition, while helpful in identifying some of the features of emotional responding, could easily be applied to a host of related constructs. Motivation, a construct that is sometimes differentiated from emotion (Stellar, 1954), also involves physiological responses, subjective cognitions or feelings, action tendencies, and cognitive interpretations. It is unsurprising, therefore, that the boundaries that differentiate emotion from other related constructs move, blur or disappear altogether depending on who is drawing them. As scientists, we must isolate

a phenomenon of interest in order to study it. These attempts to compartmentalize psychological functions into distinct categories are no doubt necessary for experimental progress; however, they are also responsible for the seemingly arbitrary boundaries that separate highly interrelated processes. Focusing on the distinctions between related psychological and neural processes may prevent us from discovering the more fundamental properties underlying them.

As one example of this problem, emotion, reward processing, and social functioning are often studied in isolation, yet they share many common features. A guided investigation of the basic psychological and neural properties that are shared among these processes could yield new insights into where these domains overlap and whether they diverge, thereby improving our understanding of both domain-general as well as domain-specific affective processes. Existing models of emotion offer a useful starting point for beginning such an investigation. Much empirical and theoretic work has fed into the development of models of emotion, and discourse about the strengths and weaknesses of these various models has been prolific. Here, I will give an overview of three major classes of models for emotion—categorical models, constructionist models, and survival circuit animal models—and I will review some of the evidence that has been used to support and contest each. Out of these three models, the constructionist framework is the most relevant for understanding commonalities among emotion, reward, and social processing; therefore, I will focus the remainder of the chapter

considering the application of the constructionist model across domains. I will review existing literature suggesting that *core affect* and *conceptualization*, which are main elements of constructionist models of emotion (Lindquist & Barrett, 2012), are manifest in neural responses across reward, emotional, and social functioning. I will then present some of the ways in which the theory that the brain encodes *domain-general affective properties* can be tested.

1.1 Contemporary Theories of Human Emotion

Throughout the history of psychology there has been much debate on the nature and genesis of emotion. Theories of human emotion typically fall into two camps, those proposing a *categorical* account of emotion and those proposing a *constructionist* one. Categorical models posit that a handful of emotions or emotional behaviors are "basic." That is, these emotions do not arise out of combinations of more general psychological processes, but are themselves distinct and fundamental psychological responses (Ekman, 1992). The vast array of complex emotions experienced by humans are built from combinations of these basic emotions and interactions with cultural learning and context (Ekman & Friesen, 1975; Tomkins & Mccarter, 1964).

Though the existence of so-called basic emotions does not necessarily imply that these emotions have evolutionary relevance (see Parkinson, 1996), most categorical models are grounded in evolutionary explanations (Ekman, 1992; Izard, 1992). Often categorical theories trace their origin back to Darwin, who described some of the

characteristic features of specific emotional responses across species in *The Expression of Emotion in Man and Animals* (Darwin, 1872/2009). Though there has been some debate as to whether Darwin's work truly aligns with what categorical emotion theorists claim today (Barrett, 2011), a key element of many categorical theories is that stereotyped physiological and behavioral responses evolved for each of the basic emotions because these response sets promoted adaptive behavior in response to particular environmental circumstances (Izard, 1992). It should follow then that basic emotions will be associated with distinct autonomic (Ekman & Cordaro, 2011) or neural profiles (Izard, 1992; Izard, 2011; Vytal & Hamann, 2010) as well as distinct outward expressions and precipitating conditions (Ekman & Cordaro, 2011; Ekman, 1992; Izard, 1992; Izard, 2011).

Perhaps the best known basic emotion model is the one posited by Paul Ekman (Ekman & Cordaro, 2011; Ekman, 1992). In a recent review, Ekman & Cordaro (Ekman & Cordaro, 2011) detailed the thirteen properties that collectively determine whether a particular emotional response can be considered "basic." These properties concern an emotional response's distinctiveness in experience and expression, automaticity, presence in non-human primates, and brief duration. Based on these features, Ekman and Cordaro conclude that there are seven basic emotions: anger, fear, surprise, sadness, disgust, contempt, and happiness. In this model, they argue that delineating these basic emotions does not mean that every response within each basic emotion category must be identical. Instead, the basic emotions are best construed as "families" that share

expression, physiology, and precipitating events. Experiences within the emotion family of happiness, therefore, may be subject to some variation based on exactly what provoked the emotion, whether it occurred spontaneously or in response to an external stimulus, or whether it is being subjected to emotion regulation. Despite this variation within a family, Ekman and Cordaro contend that the boundaries *between* emotion families are firm and non-overlapping. Thus, emotion families can be considered basic and distinct psychological phenomena.

As evidence for this perspective, Ekman and Friesen (1969) demonstrated that participants in the United States, Japan, Brazil, Argentina, and Chile all associated the same facial configuration with the same emotion label. Moreover, in a follow-up study (1971) these same authors found that preliterate participants in New Guinea who had little to no exposure to Western media associated the same facial expressions used in the previous study with particular emotional scenarios designed to elicit the associated emotion (i.e., they associated the sad facial expression from Ekman and Friesen (1969) with sadness evoking stories). Thus, the recognition of these emotions is neither culturally learned nor dependent on written language. In addition to evidence for universal recognition of basic emotion expressions, there is evidence that particular states of the autonomic nervous system differentiate the basic emotions. Levenson, Ekman, and Friesen (1990) measured skin conductance, heart rate, and finger temperature while participants voluntarily configured their facial expressions to match

basic emotional expressions. Results indicated that autonomic profiles were distinct for anger, disgust, fear, happiness, sadness, and surprise. Moreover, when participants manipulated their facial muscles to match a basic emotional expression, this triggered an experience of the congruent emotion on around 50% of trials. Ekman & Cordaro (2011) note that these particular response profiles seem to promote adaptive behavior, lending support to the theory that basic emotion categories evolved as a result of their specific survival benefit. For example, they note that anger increases blood flow to the hands and arms, which would potentially prepare an organism to fight whereas fear increases blood flow to the legs and feet, which would prepare an organism for flight.

While Ekman's model has been highly influential, other variants of categorical models exist. The model posited by Caroll Izard (Izard, 1992; Izard, 2011) is also broadly consistent with a categorical conceptualization of emotion. In his model, certain emotional responses are deemed "first order." These first-order responses, like basic emotions, are discrete from one another, are evolutionarily based, occur early in development, and do not necessitate complex cognitive processing. Based on these criteria, Izard claims that first-order emotions include interest, joy, sadness, anger, and fear. These emotions, which are primarily experienced in their pure form only during infancy and early childhood, are contrasted with "emotion schemas," which occur within conscious awareness and are the product of interactions between first-order feelings and complex higher order cognition. Izard's model contends that each of the

first-order or basic emotions has a distinct representation in the brain (Izard, 1992; Izard, 2011).

In keeping with these ideas, there have been several recent attempts to elucidate the response profiles associated with discrete basic emotions. In one meta-analysis, Lench, Flores and Beech (2011) aggregated across studies examining happiness, sadness, anger and anxiety to test for evidence of separable responses in terms of cognitions, behavior, subjective experience, and physiology. The effect sizes of differences between emotion categories were examined across the 510 articles included in the sample. The authors found evidence for a medium effect size associated with comparisons of emotion categories. In contrast, they found only weak evidence supporting the idea that emotions occur along continua of valence and arousal. Meta-analytic techniques have also been used to examine neuroimaging evidence for categorical theories of emotion. Using activation likelihood estimation (ALE), Vytal and Hamann (2010) examined the main effects of neural activation in response to fear, anger, disgust, sadness, and happiness as well as the differences between each emotion category. Both the main effects analysis and the contrasts revealed some differences in the neural profiles associated with each emotion. Based on these results, the authors concluded that existing neuroimaging literature provided broad support for the theory that basic emotions are associated with distinct neural profiles.

These conclusions, however, do not seem entirely in keeping the results from the Vytal & Hamann's analysis. Notably, in the main effects analysis, there is overlapping activation in the insula for fear, anger, and disgust. Similarly, there are overlapping activations in the medial prefrontal cortex in the main effects maps for happiness and fear. Furthermore, in the contrast analysis, different regions appear as a result of each emotion-by-emotion comparison. Though a basic emotion account does not necessarily presume that a single emotion must map to a single region of the brain, it does presume that at the very least the same profile of activation should be consistently activated in response to each category, and that these profiles should be distinct. In this study, that the maps associated with each emotion varied considerably depending on the comparison point suggests that this is not the case.

The meta-analysis performed by Lench, Flores, and Bench (2011) is also flawed, and has been criticized as providing insufficient evidence to claim support for a categorical account of emotion. Lindquist and colleagues (Lindquist, Siegel, Quigley, & Barrett, 2013) argue that to test for evidence of discrete emotional responses, Lench, Flores and Bench would need to demonstrate that responses to basic emotion categories were both specific and consistent. Because they only tested for the magnitude of differences between responses to emotion categories (indicating little about the nature of the response), their analysis does neither. That is, it is not sufficient to claim that there is a difference in galvanic skin response between sadness and happiness. Instead,

consistent differences between these emotions in the timing, magnitude, or shape of the response across many studies would be necessary to claim that the response profiles are truly distinct.

Such critiques of categorical emotion theories serve as the rallying cry of constructionist emotion theorists. Constructionist theories of emotion postulate that emotions do not fall into discrete categories, but rather are psychological events that emerge out of domain-general psychological ingredients (Gendron & Barrett, 2009; Lindquist & Barrett, 2012; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Lindquist, 2013). Exactly what ingredients are included in the recipe depends on the theory; however, most constructionist theories include some variant of three basic elements: hedonic value, arousal, and interpretation (Lindquist, 2013). The hedonic value of an emotional reaction accounts for the valence of an emotional stimulus or subjective experience (i.e., whether the stimulus or experience is pleasant or unpleasant). The arousal element of emotion captures the intensity or magnitude of an emotional response. Much as the absolute value of 100 and -100 is the same, the arousal level associated with profound joy and despair may be similar despite opposite hedonic direction. Lastly, the subjective experience of emotion is also dependent on how meaning is ascribed to hedonic and arousal responses.

These elements form the basis of the constructionist model proposed by Lisa Feldman Barrett and colleagues. In this model, emotion is comprised of two main

ingredients, *core affect* and *conceptualization*. *Core affect* is defined as, "the mental representation of bodily changes that are sometimes experienced as feelings of hedonic pleasure or displeasure with some degree of arousal" (Lindquist et al., 2012). Core affect is associated with fluctuations in bodily state in the periphery, which are represented in the brain. These changes in core affective responses interact with *conceptualization*, which ties together external sensory inputs with internal core affective reactions by taking advantage of knowledge about the world and prior experience. Conceptualization helps individuals to categorize what are otherwise abstract affective reactions by allowing them to attend to certain elements of an experience while disregarding others (Barrett, 2006; Lindquist & Barrett, 2012). To do this, humans employ language, episodic memory, and executive attention to make predictions about their own emotional states as well as the emotional states of others (Lindquist et al., 2012).

As one of the many studies Lindquist, Barrett and colleagues have performed to support this model (e.g., Barrett & Kensinger, 2010; Barrett, Quigley, Bliss-Moreau, & Aronson, 2004; Lindquist, Barrett, Bliss-Moreau, & Russell, 2006; Oosterwijk et al., 2012), Lindquist et al., (2012) performed an extensive meta-analysis of the neuroimaging literature to determine whether regions or networks encoded these psychological ingredients rather than discrete emotional responses. Though the results identified neural regions consistently activated with each emotion, they did not find evidence that neural profiles for each basic emotion were distinguishable. The authors interpreted

these findings as evidence that emotions are constructed out of more fundamental psychological ingredients that in particular combination produce specific emotional responses. Results from this study complement findings from a previous analysis (Kober et al., 2008) in which the authors did not separate studies based on the specific emotions being studied, but looked for the emergence of functional networks across studies of emotion more generally. This analysis identified six networks that the authors concluded were involved in the basic processes that collectively make up emotion. Two networks (core limbic and paralimbic) were implicated in core affect, two networks (medial prefrontal and medial posterior) were implicated in conceptualization, one cognitive/motor network was implicated in executive attention and language processes, and one network primarily made up of occipital regions was implicated in visual processing.

1.2 Survival Circuit Animal Models of Emotion

The theories and research discussed thus far in this chapter have primarily focused on the experience, expression, and fundamental properties of human emotions. Yet animal models have contributed to scientific understanding of emotion and emotional behaviors by identifying processes that are conserved in other species and by pointing to the potential evolutionary function of emotional processes. Jaak Panksepp (Panksepp & Watt, 2011; Panksepp, 2005, 2011) has proposed such a model, drawing on insights and data primarily derived from his own and others' work in animals. Though his model has

been classified as a variant of a categorical theory (Barrett, 2011), it differs from human categorical models in important ways. First, Panksepp parses emotional processes into hierarchical levels, with "primary processes" (*core affect*) arising from survival-relevant responses in evolutionarily old subcortical structures, "secondary processes" (*elaborations*) arising from classical and instrumental conditioning, and "tertiary processes" (*emotions*) arising from the complex interactions among aspects of the neocortex, limbic, and paralimbic structures. In contrast to Lindquist and Barrett's definition of core affect (Lindquist & Barrett, 2012), Panksepp posits seven core affective processes with dedicated neural circuits: "seeking" or appetitive drives guiding foraging behaviors, "fear" or basic defensive responses such as flight or freezing, "rage" or responses related to competition for resources, "lust" or sexual drives, "care" or nurturing responses, "panic/grief" or responses to separation, and "play" or social responses associated with amusement. According to Panksepp, these core affective processes and their associated neural circuitries arose because the response implemented by each conveys adaptive value. For example, when juvenile rats engage in what appears to be playful behavior (e.g., wrestling, chasing), they emit ultrasonic vocalizations (Knutson, Burgdorf, & Panksepp, 1998). The same pattern of vocal responses can be elicited by electrical brain stimulation, which rats will voluntarily engage in, and when a human experimenter "tickles" a research rat (Burgdorf, Wood, Kroes, Moskal, & Panksepp, 2007). Pankseep has used this evidence to claim that rats

engage in play behavior (Siviy & Panksepp, 2011) and even laughter (Panksepp, 2007), and that these play behaviors are crucial for helping animals learn social skills and social behavior (Panksepp, 2011).

Joseph LeDoux (2012) also proposes a model based on an understanding of animal behavior and neurocircuitry. Though his model also emphasizes circuits that promote survival, his conception differs from Panksepp's model. LeDoux notes that different evolutionary pressures may have led species to develop different behavioral reactions in response to activation of a particular survival circuit. That is, while the neural circuit responsible for survival behavior is conserved, the behavioral expression may not be. This contention differs from Panksepp's definition of survival circuits, which links strongly to fixed behavioral response sets (Panksepp, 2005). Furthermore, instead of contending that particular networks instantiate emotional processes per se, LeDoux argues that the neural circuitry responsible for survival behaviors such as defense, energy maintenance, fluid maintenance, thermoregulation, and reproduction (and potentially others) are important starting points for understanding more abstract constructs such as emotion and feelings, though they do not encode such complex responses themselves. He notes that circuits mediating these behaviors are present in animals across many species and may form the basis of higher-level affective cognition in humans. According to LeDoux, the human experience of emotions relating to survival circuits occurs when an individual becomes consciously aware that a survival circuit has

become activated in response to some opportunity or threat and appraises and labels her subjective response. LeDoux notes also that other "feelings" such as those related to social and cultural learning (e.g., guilt and pride) and those related to sensory functions (e.g., a bothersome itch) can occur in the absence of survival circuit activation.

Whether considering the model proposed by Panksepp, LeDoux, or other animal researchers, examining behaviors and responses analogous to human emotional behaviors in animals is undeniably important. Such research allows emotion-related functions to be characterized in detail at the neurochemical, cellular, and neuroanatomical level; however, there are vast organizational and functional differences between human and other mammalian brains. Thus, it has been argued that relying entirely on animal data to guide conceptions of human emotion is fundamentally limited. Furthermore, critics of Panksepp's model note that his proposed core affective circuits correspond to behaviors, not feeling states. Mapping the neural circuits responsible for freezing behavior may produce an understanding of an adaptive action tendency in response to potentially threatening stimuli, but whether this behavior can be thought of as showing a deterministic relationship with the subjective emotional experience of *fear* is not clear (Barrett et al., 2007). To understand the subjective experience of human emotion, therefore, one must take recourse to studying humans.

1.3 Extending Beyond Emotion: Application of the Constructionist Model to Reward and Social Processing

Taking categorical, constructionist, and animal models of emotion together, these theories have all helped clarify the problem of defining and studying emotion. However, of the available models, constructionist theories offer the most flexible framework for understanding affective processes beyond emotion. If emotion is constructed out of basic psychological and neural ingredients as constructionist theories contend, related processes such as reward processing and social functioning can also be understood through the lens of a constructionist model. At present comparatively few studies have attempted to build conceptual bridges between emotion, reward processing, and social functioning—subareas that have much in common but nonetheless are typically studied in isolation.

Regions of the brain (e.g., the ventral striatum, the ventromedial prefrontal cortex) typically implicated in processing stimuli that activate motivational drives and have positive hedonic value (i.e., rewards) show up in studies of social (e.g., Bartels & Zeki, 2004; Klucharev, Hytönen, Rijpkema, Smidts, & Fernández, 2009) and emotional responses (Britton et al., 2006) as well. Yet despite evidence pointing to shared neural mechanisms between reward, emotion, and social functioning, a recent semantic analysis of the frequency with which terms were jointly employed in cognitive neuroscience publications indicated that there was little overlap between commonly employed terms in neuroeconomics and other subfields (Beam, Applebaum, Jordynn,

Moody, & Huettel, in press). This discrepancy might be due in part to differing language, conceptual frameworks, and methodological practices. For example, while social and emotion neuroscience studies in humans frequently focus on evoked subjective responses (e.g., conscious emotion regulation, feelings of social rejection, assessments of the self-relatedness of particular words), neuroeconomic investigations often focus on the mathematic computations occurring in response stimuli (e.g., assessments of the probabilities and magnitudes of outcomes associated with decision variables, reward-prediction errors, delay discounting parameters). This, as well as other differences in the theory and practices of subfields, might prevent ideas from one field from flowing into the others.

Irrespective of the exact cause, the lack of common dialogue between subfields does not serve any single area whereas a shared language and framework could improve understanding of each. The constructionist theory of emotion offers a model that could serve as common ground for investigations in neuroeconomics and social and affective neuroscience. Indeed, Barrett has noted that the elements of her constructionist model can be found in other psychological processes (Barrett, 2009). The subjective responses to stimuli typically classified as emotional, rewarding, or social all engage the major components of the constructionist model posited by Lindquist, Barrett, and colleagues. That is, emotional, reward, and social responses all rely on largely overlapping networks for core affect and conceptualization. This is because the

computational processes described in neuroeconomics *do* map to subjective experiences. While the anticipation of a rewarding stimulus evoked by a visual cue is informed by prior experience with the magnitude and volatility of outcomes associated with that cue, the anticipation of reward is undeniably associated with a subjectively constructed affective state. Moreover, understanding and building predictive mathematical models about conditions that evoke subjective emotional responses (e.g., feelings of rejection and anger in response to unfair treatment in an economic game) does not detract from the authenticity of those feelings and instead could lead to a more precise model for behavior.

1.4 Neural Mechanisms of Domain-General Affective Processing

Just as emotions cannot be neatly pared down into a few simplistic responses, neither can the neural bases of affect be traced to processing in a small set of brain areas. Though one of the early pursuits of the field of cognitive neuroscience was to map brain regions to psychological functions, the field has undoubtedly moved beyond simplistic conceptions of how the brain as a whole or even singular brain regions function. With an increase in the prevalence of techniques such as independent components analysis, dynamic causal modeling, psychophysiological interaction analysis, and pattern classification, there has been a shift towards understanding how interactions within and between brain areas and subareas produce specific psychological phenomena. As a result, I will not attempt to review the vast literature on all of the brain areas and

networks potentially important to the construction of affective responses. Instead, I will provide a brief summary of the affective functions of regions of the brain relevant to subsequent chapters of this dissertation. (For a more complete discussion of regions involved in the construction of affect, see Lindquist & Barrett, 2012; Lindquist et al., 2012).

1.4.1 Neural Mechanisms of Domain-General Core Affect

Amygdala. The amygdala is a subcortical structure located in the medial temporal lobe that is made up of several interconnected nuclei (Sah, Faber, Lopez De Armentia, & Power, 2003). At the time of this writing, a Google Scholar search including the terms "amygdala" and "emotion" produces over 76,000 results (as compared to 35,800 results for "insula" and "emotion" and 12,500 results for "ventromedial prefrontal cortex" and "emotion"). Thus, there has been considerable focus on amygdalar response to emotional stimuli. Discourse on what role the amygdala plays in emotional processing, however, has evolved over time. Historically, the amygdala was implicated specifically in fear processing. In the late 1930s Heirich Kluver and Paul Bucy demonstrated that rhesus macaques that underwent temporal lobectomies demonstrated a condition they deemed "psychic blindness." These animals indiscriminately approached objects, other animals and humans without hesitation, and began exploring new stimuli orally. These behavioral changes occurred despite no apparent deficits in visual processing. The authors concluded that damage to the temporal lobe seemed to interrupt animals' fear

and anger responses (Kluver & Bucy, 1939). Later, it was discovered that these deficits occurred specifically as a consequence of damage to the amygdala (Horel, Keating, & Misantone, 1975). Since this early work, it has been repeatedly demonstrated that the amygdala is critically involved in aspects of fear learning including both the acquisition and extinction of fear conditioning (Phelps, Delgado, Nearing, & LeDoux, 2004). Moreover, human patients with bilateral amygdala lesions show specific deficits in their ability to recognize fearful facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994), and fMRI studies have shown that the amygdala is more engaged by fearful faces (Breiter et al., 1996) and fear-evocative stimuli such as snakes and spiders (Ohman, 2005) than by neutral stimuli. These findings strongly suggest that the amygdala is critical for fear processing, but they do not rule out a more general function for this region. The amygdala is also activated by a broader range of emotional stimuli including angry, sad, and disgusted facial expressions (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006) and both negatively and positively valenced scenes (Kim & Hamann, 2007; Winecoff, LaBar, Madden, Cabeza, & Huettel, 2011). Furthermore, the deficits in fear recognition observed in human patients with bilateral amygdala damage seem to disappear when patients are instructed specifically to focus on the eye region of the face (Adolphs, Gosselin, Buchanan, Tranel, & Damasio, 2005). Thus, the amygdala's response doesn't seem to be specific to fear processing per se, but rather in identifying salient stimuli in the environment.

Evidence that the amygdala is also involved in reward processing likewise suggests that this region contributes to domain-general core affective responses. Electrophysiological data in rats indicate that a substantial portion of cells in the basolateral (26%) and central nucleus (28%) responded similarly to conditioned stimuli predicting either a shock or the administration of sucrose (Shabel & Janak, 2009). Furthermore, neonatal lesions of the amygdala in rhesus macaques reduce affective reactions to both positive as well as negative videos (Bliss-Moreau, Bauman, & Amaral, 2011). Neuroimaging studies in humans have similarly pointed to a role for the amygdala in reward responses. For example, amygdala activation is associated with the anticipation of pleasant taste stimuli (O'Doherty, Deichmann, Critchley, & Dolan, 2002) and monetary rewards (Hommer et al., 2003).

In addition to both emotion and reward processing, the amygdala also appears to encode core affect in response to social stimuli. In Caucasian participants who score high on measures of implicit race bias, images of African American faces elicit greater activation in the amgydala than images of Caucasian faces (Phelps et al., 2000). Moreover, activation in the amgydala is increased when participants view images of extreme out-groups (e.g., homeless people and drug addicts) (Harris & Fiske, 2006), and when participants judge faces as less trustworthy (Engell, Haxby, & Todorov, 2007). In contrast to studies pointing to a role for the amygdala in social aversion, amygdala activation has also been observed when participants view erotic stimuli (Ferretti et al.,

2005; Hamann, 2005). Thus, in social contexts, the amygdala may be important for identifying social agents with whom interactions might have evolutionary consequences. Given the complexity of human interactions in large societies, a neural substrate that enables the tracking of social agents and their meaning is critical for reproduction and survival. This conclusion is supported by evidence that in both humans (Bickart, Wright, Dautoff, Dickerson, & Barrett, 2011) and primates (Sallet et al., 2011), amygdalar volume is correlated with social network size.

Determining the exact mechanism by which the amygdala contributes to core affect is by no means straightforward. Though a number of neuroimaging studies suggest that the amygdala encodes emotional arousal or emotional salience (Phan et al., 2003, 2004; Wilson-Mendenhall, Barrett, & Barsalou, 2013), the amygdala most likely serves a more nuanced role (Adolphs, 2010). It has been suggested that the amygdala identifies motivationally-relevant information in the external environment, signaling to other brain regions that ongoing processing is necessary to resolve any uncertainty pertaining to a particular stimulus to better predict the meaning of that stimulus in context (Adolphs, 2010; Lindquist et al., 2012). This role is relevant whether the stimulus is a reward, a social interaction, or otherwise emotionally evocative. Thus, the role of the amygdala in core affect can be considered domain-general.

Insula. The insular cortex, which is located deep inside the Sylvian fissure, is involved in a range of both affective and non-affective functions. Often the insula is parsed into anterior and posterior regions, which are separated by the central sulcus, though more detailed structures based on primate brains have also been suggested (Mesulam & Mufson, 1985). As a whole, the insula is thought to serve an integrative role, linking information coming from the viscera with sensory inputs from the external world (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010); however, in keeping with the differential connectivity of sub-regions of the insula, these sub-regions are thought to perform different though related functions (Flynn, Benson, & Ardila, 1999).

An array of studies point to a role of the anterior insula in affective processing. The anterior insula is often activated in fMRI studies using disgust-related stimuli (Calder et al., 2007; Heining et al., 2006; Jabbi, Bastiaansen, & Keysers, 2008; Wicker et al., 2003). Further, stimulation of the anterior insula in rhesus macaques produces facial expressions and physiological changes associated with the experience of disgust (Caruana, Jezzini, Sbriscia-Fioretti, Rizzolatti, & Gallese, 2011). Yet the role of the anterior insula in emotion is not constrained to disgust alone. One positron emission tomography (PET) demonstrated increased processing in the insula to sadness, anger, happiness and fear (Damasio et al., 2000). Moreover, the anterior division of the insula has also been shown to be associated with anxiety (Rauch, Savage, Alpert, Fischman, & Jenike, 1997), the anticipation of pain (Ploghaus et al., 1999; Strigo et al., 2013), social

rejection (Dewall et al., 2010), empathy (Singer, Critchley, & Preuschoff, 2009), and sexual arousal (Hamann, 2005; Stoleru et al., 1999). Studies in the field of neuroeconomics have contributed to the variety of tasks that engage the anterior insula, implicating this region in elements of risk processing (Huettel, Song, & McCarthy, 2005; Kuhnen & Knutson, 2005; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Preuschoff, Bossaerts, & Quartz, 2006; Preuschoff, Quartz, & Bossaerts, 2008).

At first blush the range of functions involving the anterior insula seem heterogeneous; however, if the neural bases underlying core affect are shared across reward, emotion, and social processing, the diversity of tasks that engage the insula is largely intuitive. In the face of uncertain circumstances in the external environment—as would be encountered during emotionally aversive situations, moral violations, risky decisions, and so forth—the brain must prepare the body to react to a variety of possible outcomes. The role of the anterior insula in affect might therefore best be described as encoding an awareness of feeling states (Craig, 2009; Craig, 2002). This conscious awareness of the self and body has been demonstrated in studies of interoception, body movement, and affective processing, but also in cognitive processes such as attention and perception (Craig 2009). How the anterior insula performs these functions likely depends on further anatomical distinction, namely between the dorsal and ventral aspects of the anterior insula. A recent analysis of reverse inference maps drawn from the online meta-analytic tool Neurosynth indicated that the ventral anterior insula was

associated with socioemotional terms such as “emotion”, “face,” and “anxiety,” while the dorsal anterior insula was associated with cognitive terms such as “inhibition” and “conflict” (Chang, Yarkoni, Khaw, & Sanfey, 2013). Thus, the ventral anterior insula may take advantage of fluctuations in bodily states to encode core affective feelings (Wager & Barrett, 2004) while the dorsal anterior insula may take advantage of representations of body states to guide the actions and the pursuit of goals (Lindquist & Barrett, 2012; Wager & Barrett, 2004).

In contrast to the anterior insula, the posterior insula is thought to be involved primarily in somatic sensation and sensorimotor processing (Craig, 2002; Wager & Barrett, 2004), but this does not preclude a role for the posterior insula in core affect. Electrical stimulation of aspects of the posterior insula triggers pain sensation in human patients (Ostrowsky et al., 2002), which dovetails with findings that activation in the posterior insula increases in response to painful heat stimulation (Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002). Based on the response profile of the posterior insula in pain processing, it has been suggested that this region may trigger affective reactions that guide subsequent motor action in response to painful or otherwise noxious stimuli (Frot, Magnin, Mauguière, & Garcia-Larrea, 2007). Thus, the posterior insula may provide sensory and motor representations that inform affective responses in the anterior insula and ultimately guide affectively motivated behavior. Thus, the anterior and posterior insula contribute to core affect by representing changes in the

somatosensory and affective state of the body across emotion, reward, and social processing.

Ventromedial Prefrontal Cortex/Medial Orbitofrontal Cortex. The ventromedial prefrontal cortex (vmPFC) and the medial orbitofrontal cortex (OFC) are located along the most medial aspects of the ventral surface of the prefrontal cortex. Early research on human patients with lesions in the vmPFC seemed to suggest that the critical function of this region was in mediating interpersonal behavior (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Eslinger & Damasio, 1985); however, subsequent animal and human work on decision-making and reward processing have indicated that the vmPFC instead is involved in reward valuation. Thus, while data from neuroeconomic studies do not invalidate the idea that the vmPFC is *important* for personality and social behavior, the functions performed by this region appeared to have more to do with the computation of domain-general hedonic value arising in interpersonal situations.

Data supporting the hedonic value hypothesis of vmPFC function come from neuronal recording and lesion studies that have utilized food and liquids as reinforcers as well as from studies that have utilized monetary and social rewards as reinforcements. Research has indicated that neurons in OFC play a role in how an animal develops predictions about upcoming rewards (Schultz, Tremblay, & Hollerman, 1998). In one investigation utilizing single cell recordings in OFC neurons, rats were

trained to associate olfactory cues with liquid reinforcements or punishments. Cells fired differentially depending on whether the anticipated outcome was a reward or a punishment, suggesting that these neurons track the expected value of the upcoming stimulus (Schoenbaum, Chiba, & Gallagher, 1998). As with studies in the animal literature, many neuroimaging experiments have utilized reinforcement learning tasks to characterize the neural mechanisms of outcome processing. In a classical conditioning paradigm, human participants learned to associate visual cues with the delivery of unpleasant, neutral, or pleasant tastes. Paralleling electrophysiological data in animals, the OFC tracked increasing value of anticipated outcomes. Specifically, the OFC displayed greater activation in response to pleasant than to unpleasant tastes, and greater activation in response to pleasant than to neutral tastes (O'Doherty, Deichmann, Critchley, & Dolan, 2002).

The role of the vmPFC in processing hedonic value, however, is not constrained to primary reinforcers. Both neuroimaging (Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001) and lesion studies (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Damasio, & Damasio, 1994; Rolls, Hornak, Wade, & McGrath, 1994) indicate that the vmPFC is important for processing monetary rewards. Furthermore, the vmPFC is also engaged when participants view attractive images of faces (Aharon et al., 2001; Cloutier, Heatherton, Whalen, & Kelley, 2008; O'Doherty et al., 2003; Smith et

al., 2010) and experience positive emotions (Cunningham, Johnsen, & Waggoner, 2011; Goel & Dolan, 2001; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Vrtička, Sander, & Vuilleumier, 2011). One potential unifying explanation for the plethora of pleasant stimuli that engage the vmPFC is that the vmPFC encodes subjective value across domains, creating a common neural currency for hedonic value. Two studies (Levy & Glimcher, 2011; Smith et al., 2010) indicated that activation in the vmPFC seemed to encode the "exchange rate" between rewards from different modalities (e.g., food versus money versus social rewards), which supports the idea that the vmPFC is the final site in which value is represented.

Evidence from studies of reward processing and decision making have demonstrated that the ventromedial prefrontal and medial OFC play an integral role in the computation of value signals, and further, that the value signals in this region are scaled so that disparate rewards can be encoded and compared. While this notion has served as a catalyst for many seminal neuroeconomic studies, it has had limited impact on related fields such as affective neuroscience. Yet findings from studies of emotion and positive affect broadly construed suggest that the vmPFC does not simply compute value signals for stimuli that have obvious motivational relevance. Rather, this neural system is involved in the valuation of affectively-relevant stimuli in general. This conception of vmPFC/OFC function fits with the hypothesized role of this region in a

constructionist model of emotion, namely that it is critical for hedonic value computations in core affect (Lindquist & Barrett, 2012; Lindquist et al., 2012).

1.4.2 Neural Mechanisms of Domain-General Conceptualization

Dorsolateral and Ventrolateral Prefrontal Cortex. In addition to commonalities in the brain regions responsible for encoding domain-general core affect, there is also ample evidence supporting the hypothesis that overlapping neural mechanisms are responsible for conceptualization across emotion, social, and reward domains. That is, the mechanisms by which prior learning, current goals, attention, and language are integrated to situate the experience of core affect in context are domain general. Automatically deployed biases in attention, heuristic processing, and implicit memory can influence affective feeling states and behavior in response to these feelings, and these processes and their neural mechanisms are important elements of conceptualization; however, affective responses can also be heavily altered by conscious attempts to regulate feelings. When individuals engage in reappraisal, which is one strategy for consciously altering affective responses, activations are observed in many aspects of the brain including the medial frontal gyrus, the superior parietal lobule, and the middle temporal gyrus. Yet neural activation during reappraisal is most consistently seen in the dorsolateral and ventrolateral prefrontal cortex (Ochsner, Silvers, & Buhle, 2012).

In one investigation, we demonstrated that the dlPFC and vlPFC are engaged by reappraisal of emotionally positive and negative stimuli (Winecoff et al., 2011). In our study, 20 older adults (mean age=69 years) and 22 younger adults (mean age = 23 years) underwent functional magnetic resonance imaging (fMRI) while they were shown positive, negative, and neutral photographs. On each trial, participants were instructed to either experience their emotions naturally or attempt to regulate their emotional responses by employing a detachment reappraisal strategy. Results indicated that across subjects, whereas experiencing emotions activated the amygdala, reappraisal activated the dorsal and ventrolateral prefrontal cortex as well as the dorsomedial prefrontal cortex and the inferior parietal lobule (Figure 1). Consistent with the hypothesis that aspects of lateral prefrontal cortex down-regulate responses in regions implicated in emotional arousal, psychophysiological interaction analysis indicated that regulation-related decreases in activation in the amygdala were associated with increases in activation in the left ventrolateral and dorsolateral prefrontal cortex (Figure 2).

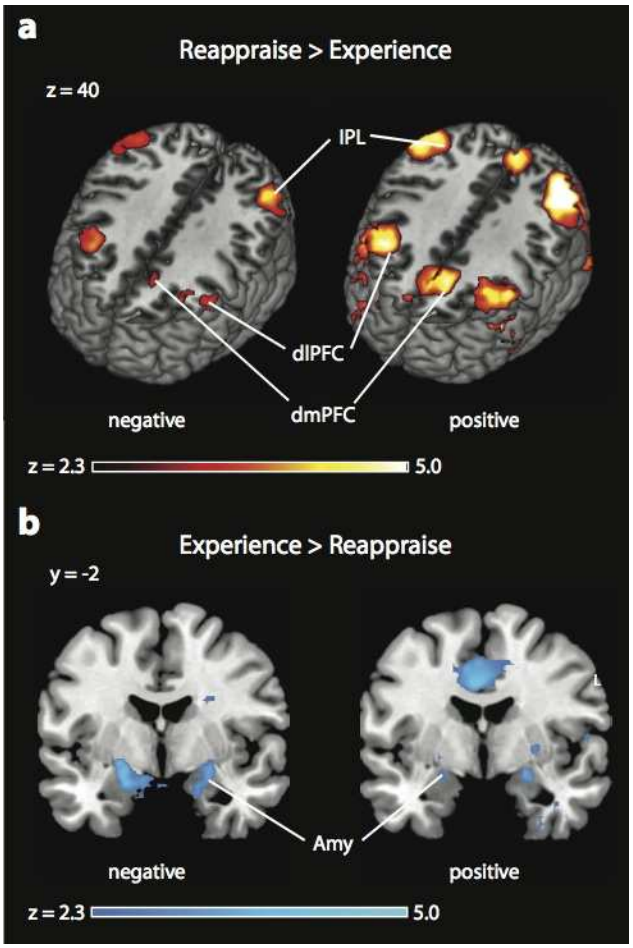

Figure 1: Neural correlates of cognitive reappraisal and emotional experience. (A) The contrast of *Reappraise* > *Experience*, collapsed over conditions and age groups, revealed that activation in dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), ventrolateral PFC (vlPFC) and the inferior parietal lobule (IPL) increased when participants engaged in reappraisal. (B) Conversely, the contrast of *Experience* > *Reappraise* revealed that activation in the amygdala (AMY) was increased during emotional experience.

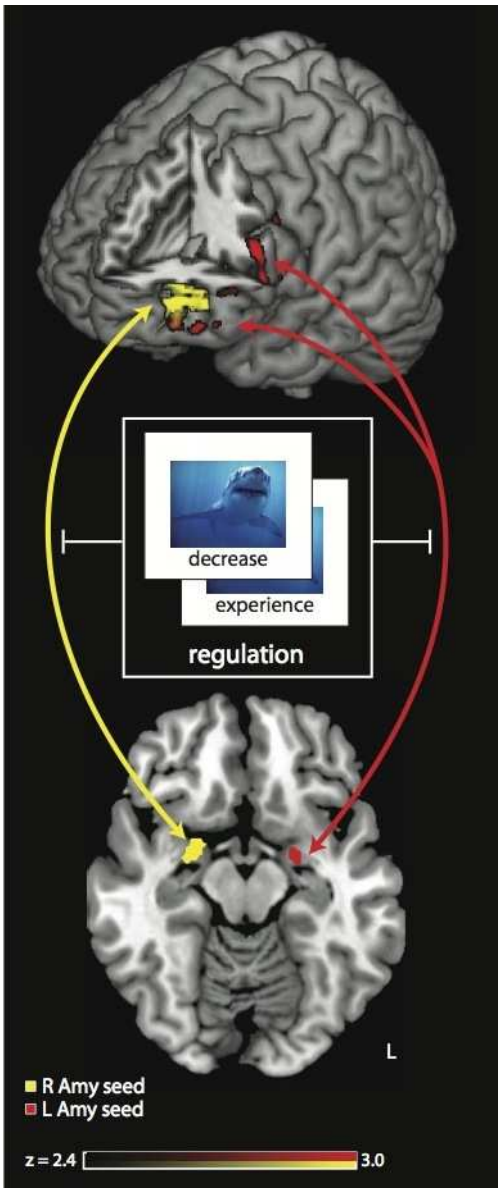

Figure 2: A psychophysiological interaction (PPI) between amygdala and lateral prefrontal cortex. Using the left and right amygdala as seed regions, we found significant PPI effects in the left ventrolateral prefrontal cortex.

The dorsolateral prefrontal cortex and the ventrolateral prefrontal cortex have been implicated in other aspects of cognitive control such as working memory and

response inhibition. Moreover, the process of reappraisal also taps these functions—keeping the current regulation goal in mind while actively implementing reappraisal, inhibiting bottom-up emotional arousal. Thus, it makes intuitive sense that there is considerable overlap between the regions thought to perform these cognitive functions and those engaged by cognitive reappraisal (Ochsner & Gross, 2005; Ochsner, Silvers, & Buhle, 2012). While the role of the dorsal and ventrolateral prefrontal cortex in regulating emotions has been well-established (Buhle et al., 2013), there are also a growing number of studies documenting the role of these regions in regulating responses to rewards. The use of modified reappraisal strategies during the anticipation of reward has been associated with decreases in activation in the ventral striatum. Moreover, the regulation of reward expectancy has been shown to recruit the dorsolateral and ventrolateral prefrontal cortex (Delgado, Gillis, & Phelps, 2008; Staudinger, Erk, Abler, & Walter, 2009; Staudinger, Erk, & Walter, 2011) as well as the inferior parietal lobule/temporoparietal junction (Staudinger et al., 2009, 2011). In addition to neural changes, behavioral changes in reward processing also occur in response to emotion regulation. For example, emotion regulation alters risk-seeking behavior (Heilman, Crisan, Houser, Miclea, & Miu, 2010; Martin & Delgado, 2011).

Beyond emotion and reward-evoked responses in non-social situations, the ventrolateral and dorsolateral prefrontal cortices also seem to regulate affectively-motivated behavior in social contexts. Retaliatory behavior in responses to unfair

treatment in the ultimatum game is associated with activation in the insula (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; Tabibnia, Satpute, & Lieberman, 2008); however, when a participant chooses to accept an unfair offer, the ventrolateral prefrontal cortex shows an increase in activation (Tabibnia et al., 2008). This activation may be an implicit indication of emotion regulatory processes operating to suppress the desire to retaliate in favor of making a more financially beneficial choice. Van't Wout and colleagues supported this conclusion by examining the effect of explicitly deployed cognitive reappraisal on behavior in the ultimatum game (Grecucci, Giorgetta, van't Wout, Bonini, & Sanfey, 2012; van't Wout, Chang, & Sanfey, 2010). When asked to reappraise emotional responses to ultimatum game offers, participants were more likely to accept unfair proposals. Furthermore, this shift in behavior during regulation was associated with increased activation in the ventolateral and dorsolateral prefrontal cortex (Grecucci et al., 2012). Notably, the dorsolateral prefrontal cortex is also activated when individuals make emotionally difficult but utilitarian moral judgments, (Greene, Nystrom, Engell, Darley, & Cohen, 2004), suggesting that this region may act to inhibit affective responses that might otherwise interfere with decisions to optimize the greater good. Collectively, results across fields suggest that affective reactions induced by rewards or social situations can be altered by emotion regulation in much the same way as emotional reactions. Further, the dorsal and ventrolateral prefrontal cortices seem to

be important for down-regulating responses in regions of the brain involved in core affect, irrespective of domain.

1.5 Summary

The constructionist model of emotion offers a useful framework for exploring affect broadly construed. I hypothesize that the representation of core affect as well as conceptualization relies on common neural processes across emotional, reward, and social domains. Basic science approaches offer one avenue to explore this hypothesis. To test the idea that core affective processes are shared, participants undergoing neuroimaging could be asked to make valence and arousal ratings of stimuli across domains (e.g., social images, emotional images, and monetary rewards). If responses in particular regions scaled with arousal and valence ratings across domains, a domain-general affect theory would be supported. In Chapter 2, I will describe a variant of such a study, which examined the representation of emotional valence in the vmPFC, a region of the brain that has been implicated in translating reward value across reward modalities. Taking a similar approach, other studies could be performed to examine common neural mechanisms for conceptualization. For example, if subjects were asked to use cognitive strategies such as selective attention or reappraisal to control responses to different domains of stimuli, and these processes seemed to engage neural circuitry in a similar fashion, this would support the idea that the mechanisms of conceptualization are likewise shared.

In addition to basic science investigations, studies of clinical populations could also provide support for a domain-general model of affect. Specifically, if the neural mechanisms for processing core affect and conceptualization are shared across reward, emotion, and social functioning, psychiatric disorders characterized diagnostically by disruptions in one domain should also be associated with similar disruptions in the others. Anorexia nervosa (AN) is one psychiatric disorder displaying such a pattern of psychopathology. In Chapter 3, I will review evidence that AN is characterized by common affective disruptions that manifest in emotional, reward, and social functions. I will also discuss evidence that the neural mechanisms responsible for representing core affect show altered functioning across reward, social, and emotional tasks. In Chapter 4, I will present a study showing that eating disorder symptoms are associated with altered core affective processing. In Chapter 5, I will expand further on these ideas by presenting a study examining the potential mediating role of affective biases between eating disorder symptoms and interpersonal deficits. Lastly, in Chapter 6, I will summarize and offer some potential extensions of these results.

2. Ventromedial Prefrontal Cortex Encodes Emotional Value[1]

A domain-general model for affect predicts that the neural mechanisms responsible for encoding core affect across reward, emotional, and social processing will be largely overlapping. Furthermore, in this model, how the computations involved in core affect are performed in the brain should likewise be similar across domains. One test of this theory is to investigate the degree to which neural regions known to encode aspects of core affect in one domain (e.g., reward) also encode core affect in another domain (e.g., emotion). Here, we show that the ventromedial prefrontal cortex (vmPFC), which has been strongly implicated in encoding the subjective value of rewards, also encodes the subjective hedonic value of emotional stimuli.

2.1 Introduction

Characterizing how the brain evaluates rewarding stimuli has been one of the central goals of the field of neuroeconomics. Single-unit recording studies in animals (Monosov & Hikosaka, 2012; Wallis, 2011) and functional neuroimaging studies in humans (Smith & Huettel, 2010) support the idea that reward-related computations occur in the ventromedial prefrontal cortex (vmPFC), and that activity in this region does not reflect objective properties of rewards (but see Padoa-Schioppa & Assad, 2008), but rather subjective value (Kable & Glimcher, 2007). Several investigations have

[1] This chapter is drawn primarily from a coauthored publication published in the *Journal of Neuroscience* (Winecoff et al., 2013).

suggested that the vmPFC encodes the subjective exchange rate between different reward modalities (e.g., food versus social rewards) (Chib, Rangel, Shimojo, & O'Doherty, 2009; Levy & Glimcher, 2011; Levy & Glimcher, 2012; Rangel & Hare, 2010). It thereby creates a "common neural currency" for reward (Montague & Berns, 2002), allowing disparate rewards to be compared. This signal also facilitates judgments of value to be extended beyond canonical rewards. For example, the vmPFC has been shown to respond to emotional stimuli that generate positive affect (Cunningham et al., 2011; Goel & Dolan, 2001; Vrtička et al., 2011), which suggests a domain-general role for the vmPFC in signaling the presence of motivationally-attractive stimuli (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009).

Though evidence from decision neuroscience strongly suggests that the vmPFC encodes subjective hedonic value, this view is seemingly inconsistent with results arising from studies of the neural mechanisms of emotion regulation. A recent meta-analysis indicated that across several studies using cognitive reappraisal, fear extinction, or placebo manipulations, regulating negative emotions led to converging activation within a subregion of the vmPFC (Diekhof, Geier, Falkai, & Gruber, 2011). Thus, one plausible interpretation of the function of the vmPFC is that it implements cognitive control over emotional reactions. Because this meta-analysis only included investigations on the regulation of negative affect, an alternative explanation remains: the increased signal in the vmPFC reflects the change in emotional hedonic value

following emotion regulation. Consistent with a domain-general account of affective processing, fMRI data have indicated that when participants regulate affective responses to monetary rewards, aspects of the prefrontal cortex similar to those activated by the regulation of negative emotion are engaged (Delgado et al., 2008; Staudinger et al., 2009, 2011); however, only a handful of studies have examined the neural mechanisms of positive emotion regulation (Heller et al., 2009; Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011; Winecoff et al., 2011). Investigating the encoding of hedonic value in the vmPFC during the experience and regulation of positive as well as negative emotional stimuli would reconcile disparate research conclusions from neuroeconomics and affective neuroscience about vmPFC function. To understand whether the vmPFC plays a regulatory (i.e., conceptualizating) or a hedonic value (i.e., core affective) role during emotion experience and regulation, we scanned two groups of participants while they utilized cognitive reappraisal to regulate their emotional responses to positive and negative emotional images.

2.2 Materials and Methods

We analyzed data from two experimental samples collected with similar experimental tasks and imaging parameters. Our experimental sample (Exp1) was newly collected for this study, and we validated our results in a replication sample (Exp2) drawn from a previously published study (Winecoff et al., 2011). Experimental parameters were nearly identical between the two experiments. Where differences are

present, we indicate the parameters for Exp1 in the main text and then list the parameters for Exp2 in brackets following.

2.2.1 Participants

Participants in Exp1 were 31 younger adults between the ages of 19 and 40 (M=25; 10 males). Participants reported no history of psychiatric or neurological problems or contraindications to fMRI scanning. Exp2 was made up of 20 older adults between the ages of 59 and 73 (M=69; 10 males) and 22 younger adults between the ages of 19 and 33 years (M=23; 11 males). In addition to meeting all the exclusion criteria for Exp1, all participants in Exp2 also scored at 27 or higher on the Folstein Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). The vast majority of fMRI studies have constrained their samples to healthy younger adults. Interpretation of these results therefore cannot necessarily be extended to a more general demographic. Including both younger and older adults in the Exp2 dataset ensures that the results hold not only for a typical fMRI sample, but are valid for inferences on a broader population in which there is more variance.

In both experiments, participants were paid $20/hour for time in the scanner and $10/hour for time outside the scanner. Each participant provided written consent for a protocol approved by the Institutional Review Board of Duke University Medical Center.

2.2.2 Emotion Regulation Paradigm

While undergoing scanning, participants completed a cognitive reappraisal task. Prior to beginning the fMRI task, participants were extensively trained to perform emotion regulation using a cognitive reappraisal strategy. For the Regulation condition, participants were instructed to imagine themselves as an objective observer to the situation depicted or to imagine the event as having no personal relevance to them. These instructions are consistent with prior research using a "self-focused" or "detachment" reappraisal strategy (Goldin, McRae, Ramel, & Gross, 2008; Kalisch et al., 2005; Ochsner et al., 2004; Shiota & Levenson, 2009). For the Experience condition, participants were instructed to experience their emotions naturally. During training, participants verbally reported their responses on both regulate and experience trials to the experimenter to signal that they understood the task. After this training, but before undergoing scanning, each participant completed practice trials with the same timing as the fMRI task.

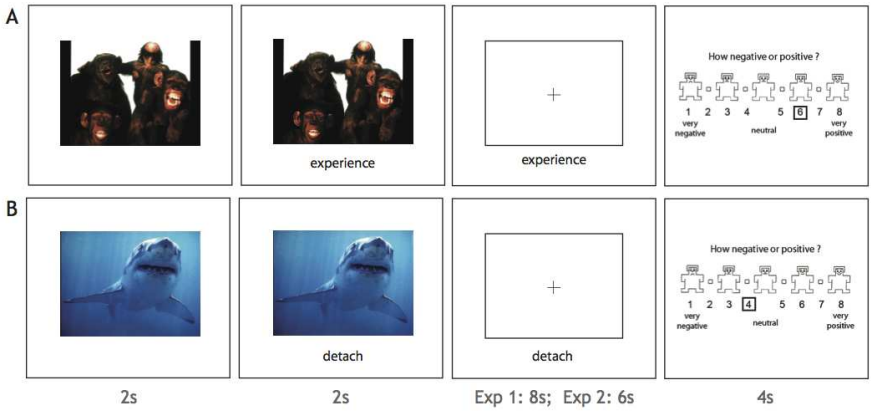

Figure 3: Reappraisal Task. (A) During Experience trials, participants viewed the image then saw a cue to experience their emotional reaction to the image naturally. Participants were asked to continue to experience their emotions even after the image disappeared. After each trial, participants rated the valence of the image. (B) During Regulate trials, participants were asked to emotionally detach themselves from the image.

In the fMRI task (Figure 3), participants were presented with images from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008) and were asked to either regulate their emotions using cognitive reappraisal (Regulate Condition) or to experience their emotions naturally (Experience Condition). Pictures were categorized as positive, negative, or neutral based on the normative IAPS ratings (valence: positive *M*=6.8; negative *M*=2.4; neutral *M*=5 [Exp2: 7.3, 2.5, 5.1]. Positive and negative images were roughly matched for arousal (positive *M*=5.8; negative *M*= 5.8 [5.6, 5.4]), and each condition had equal numbers of images with and without people.

At the beginning of each trial, a picture appeared on screen for two seconds. A cue ("Experience" or "Detach") [Exp2: "Experience" or "Decrease"] would then appear

below the image for two seconds to indicate which strategy to use. The picture would then disappear and be replaced by a fixation cross, and the cue would remain on screen for an additional 8s [Exp2: 6s]. At the end of each trial, participants were asked to rate how positive or negative they felt after having implemented the strategy. Inter-trial intervals were a minimum of 4s (range: 4-13s) and were exponentially distributed [Exp2: 0-8s in 2s intervals]. Participants viewed 125 total images evenly distributed across the five trial types (25 Positive-Experience, 25 Negative-Experience, 25 Positive-Reappraise, 25 Negative-Reappraise, 25 Neutral-Experience) over the course of five runs [Exp2: 150 total trials, 30 trials per trial type, 6 runs]. Image presentation was pseudo-randomized such that within each run participants saw equal numbers of pictures in each of the five trial types, but the order of presentation was randomized within each run. Whether each image was assigned to the reappraisal or experience condition was counterbalanced across participants. Stimuli were presented using the Psychophysics Toolbox 3 in MATLAB (Brainard, 1997).

2.2.3 fMRI Acquisition & Preprocessing

We acquired functional data on a General Electric 3T scanner with a gradient-echo inverse-spiral pulse sequence using standard scanning parameters (repetition time (TR)=2000 ms; echo time (TE)=30 ms; field of view (FOV)=256 mm; flip angle=60°; 30 axial slices parallel to the AC–PC plane; voxel size= 4 x 4 x 4mm; [Exp2: 4T scanner, TE=31ms; flip angle=90°, 34 slices, voxel size=3.75 x 3.75 x 3.8mm). Each run contained

288 [Exp2: 238] volumes of data (first six volumes discarded). A high-resolution inversion-recovery prepared SPGR anatomical image was used for normalization and co-registration of the functional data (TR=7.48ms; TE=2.98ms; whole brain coverage with 1 x 1 x 1mm voxels; [Exp2: TR=12.3; TE=5.5ms]).

FMRI data were analyzed using FSL 4.1.8 FEAT Version 5.98 (Smith et al., 2004). Preprocessing included motion correction using MCFLIRT, brain extraction, spatial smoothing using an isotropic Gaussian kernel of 6mm (FWHM), and high-pass filtering (> 100s). Functional images were normalized using transforms estimated from each participant's own high-resolution anatomical image and FSL's Montreal Neurological Institute (MNI) template using FLIRT (6 degrees of freedom for registration to participant's main structural image, 12 degrees of freedom for registration to standard space). All reported results survived full whole-brain correction (individual voxel threshold $z>2.3$; cluster-corrected significance threshold: $p<0.05$). All coordinates are reported in MNI space, and brain figures were created using MRIcron (Rorden, Karnath, & Bonilha, 2007).

2.2.4 fMRI and Behavioral Analysis

We utilized FSL's general linear model (GLM) to assess the influence of our behavioral manipulation on brain activation. First-level models corrected for local autocorrelation (Woolrich, Ripley, Brady, & Smith, 2001) and assessed brain responses to all trials within an explanatory variable within a single run. At the second level we used

a fixed-effects model to combine the data across all runs within a single participant. At the third level we used a mixed-effects analysis (FLAME 1) to model effects across all participants (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). For all imaging data, runs with more than five volumes with movement of greater than 1mm in any direction were discarded to ameliorate any contributions of head motion (6.5% of data discarded; [Exp2: 14.3%]). For all analyses not performed within FSL, we utilized SAS version 9.3.

In our first analysis ("Effect of Emotion Experience and Regulation"), we investigated the basic behavioral and neural effects of emotion experience and regulation. For our behavioral analysis, we implemented a repeated measures multi-level model in which we modeled valence and condition as fixed effects and participant as a random effect. We utilized a restricted maximum likelihood estimation method and a variance components covariance structure. For the fMRI analysis, we modeled valence and condition. We created one regressor of interest for each trial type ("Experience-Positive," "Experience-Negative," "Regulate-Positive," "Regulate-Negative," and "Experience-Neutral"), which modeled the 8s [Exp2: 6s] implementation period. Nuisance regressors were included in the model for the initial presentation of the picture and for the response period. All regressors were convolved with a standard double-gamma hemodynamic response function.

In our second model of the effects of emotion regulation and experience, we sought to characterize participants' subjective emotional responses. To do so we utilized a parametric model including participants' own trial-by-trial ratings of the valence of stimuli. We collapsed across valence (e.g., positive and negative) and examined the effect of trial-by-trial ratings within each regulation condition (e.g., Experience vs. Regulate). The amplitude of the event-related response was modulated by participants' ratings for each image. The parametric regressor was orthogonalized to the main effect to examine activations that specifically scaled with valence ratings. We also included a quadratic regressor, constructed by squaring the parametric regressor, to control for the effect of any non-linear results.

We also tested the possibility that neural responses may differ across conditions based on the normative IAPS ratings for the stimuli. In this analysis ("Neural Response to Normative Valence by Condition"), we used a repeated multi-level model using mean-centered IAPS normative ratings and regulation condition as fixed effects and participant as a random effect. We then tested whether IAPS ratings, condition, and their interaction predicted activation in the vmPFC. An ROI in the posterior vmPFC (pvmPFC) was defined based on coordinates (x=6, y=26, z=-14) drawn from a previous study of the subjective exchange rate between monetary rewards and attractive faces (Smith et al., 2010). Using the methods for single trial analysis described by Mumford and colleagues (2012), a first-level model was created for each trial for each participant

using the 8s implementation period [Exp2: 6s]. In each first-level model, nuisance regressors were included to model all other trials, the initial picture presentation, and the response phase. FSL's motion outliers function was used to identify bad timepoints. Trials corresponding to these timepoints were excluded from this analysis. Signal was then extracted from the pvmPFC ROI.

In our final analysis ("pvmPFC Activation is Associated with Differences in Behavioral Ratings"), we examined whether activation in the pvmPFC would predict trial-by-trial valence ratings even after accounting for IAPS normative ratings, regulation condition, and the interaction of ratings and condition. We constructed a GLM including experiment number, IAPS normative ratings, condition, and the trial-by-trial pvmPFC betas used in the previous analysis as independent variables and trial-by-trial valence ratings as the dependent variable.

2.3 Results

2.3.1 Effects of Emotion Experience and Regulation

We first tested whether participants' ratings differed as a function of valence (Positive vs. Negative) and condition (Regulate vs. Experience). In both experiments, there was a main effect of valence (Exp1:$F(2,2981)=2217.36$; $p < 0.0001$ & Exp2: $F(2, 4995)=3266.72$; $p <0.0001$). In Exp2 there was an effect of condition ($F(1,4995)=9.83$; $p=0.0017$), and in both experiments there was a valence by condition interaction (Exp1: $F(1,116)=27.05$; $p <0.0001$ & Exp2: $F(1,160)=4.496$; $p =0.04$), such that regulation led to

more positive ratings (i.e., more neutral) for negative stimuli, but less positive (i.e., more neutral) ratings for positive stimuli (Exp 1: Positive-Experience, *M*=6.328, SE=0.057; Positive-Reappraise, *M*=5.068, SE:0.035; Neutral-Experience *M*=5.044, SE=0.046; Negative-Reappraise *M*=3.360, SE=0.0375; Negative-Experience *M*=2.211, SE=0.0375. Exp 2: Positive-Experience, *M*=6.232, SE=0.042; Positive-Reappraise, *M*=5.151, 0.042; Neutral-Experience *M*=5.145, SE=0.046; Negative-Reappraise *M*=3.331, SE=0.042; Negative-Experience *M*=2.464, SE=0.044).

We then tested whether ratings differed between valenced stimuli (Positive vs. Negative) that had been regulated and neutral images that had been experienced. In both experiments there was a significant overall effect of valence category (Exp1: $F(2,87)=5.71$; $p=0.005$ & Exp2: $F(2,120)=43.21$; $p<0.0001$). Follow-up tests indicated that regulated-negative versus regulated-positive stimuli were rated significantly different from each other (two-sided paired t-tests: Exp1: $t(30)=54.47$; $p<0.0001$; Exp2: $t(41)=22.88$; $p<0.0001$) and that both regulated-positive as well as regulated-negative stimuli were rated differently from neutral stimuli (Exp1: neg: $t(41)=-20.42$ $p<0.0001$; pos: $t(41)=5.65$; $p<0.0001$; Exp2: neg: $t(41)=-71$; $p<0.0001$; pos: $t(41)=4.71$; $p<0.0001$). These results indicate that, for both positive and negative stimuli, regulation was successful in changing the subjective experience of hedonic value but did not completely neutralize emotional responses (Figure 4).

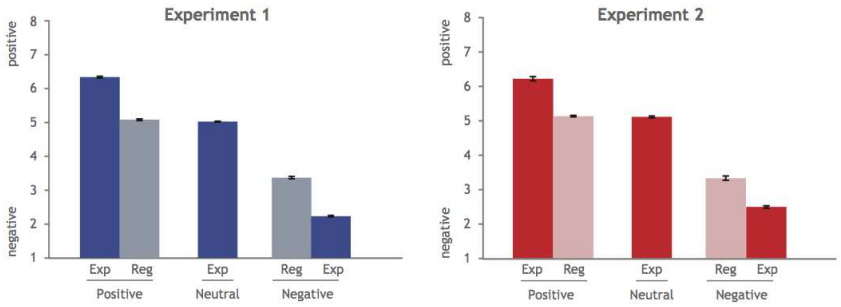

Figure 4: Valence ratings by task condition. In both Exp 1 and Exp 2, stimuli in the Regulate (Reg) condition were rated as less emotionally evocative than images in the Experience (Exp) condition. Error bars represent standard error of the mean within subjects.

In our imaging data, negative regulation (Negative-Regulate > Negative-Experience) activated regions of the prefrontal cortex including the inferior frontal gyrus, the middle frontal gyrus, and the superior frontal gyrus (see Table 1 for activation coordinates). In addition, regulating negative emotion led to increased activation in the posterior cingulate cortex and the angular gyrus. In contrast, negative experience (Negative-Experience > Negative-Regulate) revealed no significant overlapping activations between the two experiments.

Positive regulation (Positive-Regulate > Positive-Experience) was associated with increased activation in regions of the prefrontal and parietal cortex including the middle frontal gyrus, the inferior frontal gyrus, and the angular gyrus. Conversely, positive emotion experience (Positive Experience > Positive-Regulate) was associated with activation in the bilateral amygdala and the vmPFC in both experiments. Thus, emotion

regulation reduces vmPFC activation compared to that observed during emotion experience (Figure 5a; vmPFC peak activations within overlap, Exp1: max Z=4.88, x=4, y=22, z=-4; Exp2: max Z=4.61, x=-4, y=44, z=-6).

Table 1: Cluster peaks for emotional experience or regulation. x, y, z = coordinates of peak voxel, shown in MNI space. Max Z = z-statistic of peak voxel.

Experiment 1			**Experiment 2**		
Anatomical Label	***x, y, z***	**Max *Z***	**Anatomical Label**	***x, y, z***	**Max *Z***
Positive Experience > Positive Regulate					
subcallosal gyrus	4,22,-2	5.24	frontal pole	-8,56,2	5.35
			frontal pole	-6,62,6	5.11
			paracingulate	-8,52,10	5.21
			paracingulate	-4,42,-6	4.81
			occipital pole	24,-98,8	4.81
			lingual gyrus	-4,-88,-10	3.97
			postcentral gyrus	-46,-22,28	5.09
			SMA	-8,-8,46,	4.83
			postcentral gyrus	-44,-26,34	4.58
			cingulate	-4,-2,36	4.33
			parietal operculum	-48,-28,24	4.15
Increasingly Positive Valence					
medial frontal gyrus	-6,34,-16	4.69	paracingulate	2,42,-8	4.79
			paracingulate	4,46,-6	4.71
subcallosal gyrus	-2,20,-16	4.47	frontal pole	-6,70,6	4.2
			precuneus	0,-66,22	3.58
subcallosal gyrus	-6,28,-14	4.39	precuneus	22,-54,6	4.1
			precuneus	10,-62,18	3.23
precuneus	-2,-62,20	4.16	posterior cingulate	14,-48,4	3.59
precuneus	-8,-54,6	4.01			
precuneus	-16,-50,4	3.78	lingual gyrus	18,-50,0	3.55
			supracalcarine cortex	-18,-64,12	3.4
Positive Regulate > Positive Experience					
frontal pole	34,58,-8	4.25	precuneus	0,-74,42	5.02
frontal pole	-44,50,-10	4.51	angular gyrus	60,-52,34	5.66
inferior frontal gyrus	-52,28,-4	3.59	angular gyrus	64,-48,24	4.14
			angular gyrus	48,-52,32	5.85
angular gyrus	52,-48,38	4.8	lateral occipital	50,-62,42	4.78

angular gyrus	48,-48,34	4.57	cortex		
angular gyrus	62,-54,32	4.45	inferior frontal		
lateral occipital cortex	48,-60,52	4.39	gyrus	-38,24,20	5.41
			lateral occipital cortex	-38,-62,38	5.9
angular gyrus	-50,-60,30	4.27	middle temporal		
angular gyrus	-48,-52,44	4.93	gyrus	-62,-44,-4	4.42
lateral occipital cortex	-42,-64,46	5.32	middle frontal gyrus		
frontal pole	6,42,54	4.09	middle frontal gyrus	42,22,36	5.71
lingual gyrus	46,24,36	5.49			
middle frontal gyrus	-42,18,34	4.5	middle frontal gyrus	-46,14,44	5.59
middle frontal gyrus	-38,20,40	4.19	superior frontal gyrus	-44,16,30	5.32
middle frontal gyrus	-36,12,52	4.04		0,24,50	5.7
Negative Experience > Negative Regulate					
none			occipital pole	28,-100,8	4.15
			parietal operculum	48,-22,26	4.3
			hippocampus	-20,-2,-12	4.34
			postcentral gyrus	-64,-20,20	4.32
Negative Regulate > Negative Experience					
superior frontal gyrus	-2,26,50	5.29	inferior frontal gyrus	-54,20,2	5.45
lateral occipital cortex	-48,-68,48	4.89	lateral occipital cortex	-40,-66,42	4.45
			insular cortex		
posterior cingulate	-2,-26,24	5.29	middle frontal cortex	40,20,-4	3.91
				36,22,38	4.07
angular gyrus	44,-56,30	5.72			
middle temporal gyrus	-62,-38,-10	4.88			

To assess the relationship between vmPFC activation and subjective experiences of positive emotion, we also interrogated the effects of participants' own trial-by-trial ratings of stimuli. This model tested the possibility that, like reward, emotional value is encoded in the vmPFC as a continuous, graded signal. For stimuli in the Experience condition, activation in the vmPFC increased with increasing ratings of positivity (Figure 5b). In the same model for regulated stimuli, however, there were no significant activations. One potential explanation for this result is that post-regulation, stimuli in both the positive and negative regulation condition clustered around neutral valence ratings. Thus, if the vmPFC does track final hedonic value, we would not expect its activation to vary in conditions in which the subjective experience of emotion is essentially constant. Alternatively, it is possible that the encoding of emotional value during emotion regulation shifts to another area of the brain. Given the reduced variability in ratings in the regulation condition, it is not possible to distinguish between these two explanations.

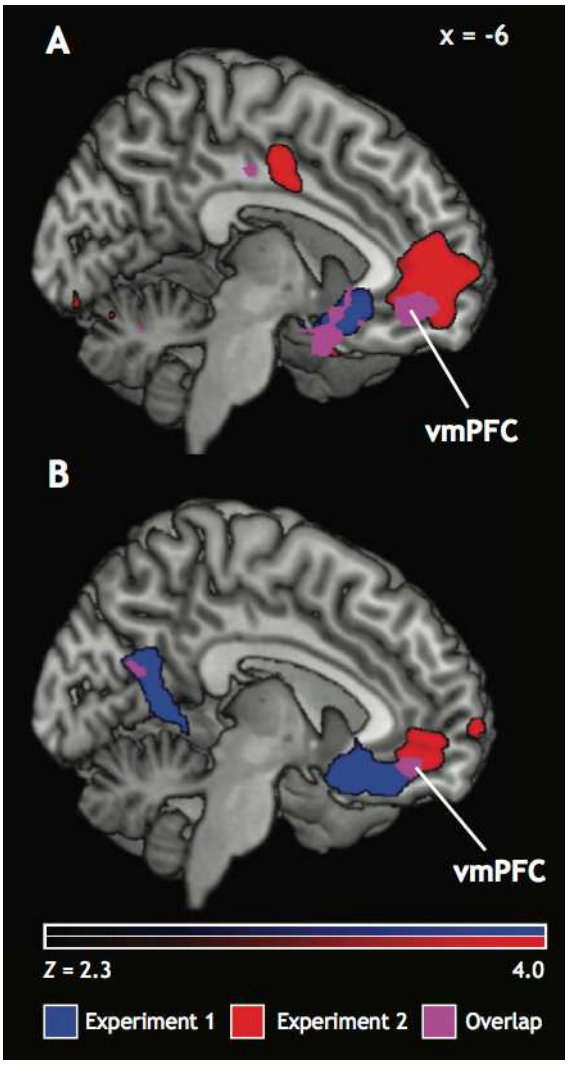

Figure 5: Neural mechanisms of positive emotion. (A) The contrast of Positive-Experience > Positive-Regulate for both Exp1 and Exp2 revealed an overlapping activation in the vmPFC. (B) A parametric model using participants' trial-by-trial valence ratings showed that increasingly positive valence ratings were associated with increased activation in the vmPFC in the Experience condition.

2.3.2 Neural Response to Normative Valence by Condition

We next tested whether normative IAPS ratings as well as condition would predict trial-by-trial estimates of activation in the pvmPFC. Given that the IAPS picture set has been rated by thousands of participants (Lang et al., 2008)—and that normative ratings for each stimulus were highly predictive of our participants' ratings of each stimulus (Experience Condition: r=0.785; Regulate Condition: r=0.707)—we took normative valence ratings to represent a typical response to these stimuli. We then tested whether those normative ratings had differential effects upon activation in pvmPFC, contingent upon the regulation condition. There was a marginally significant main effect of IAPS normative rating (F(1,7982)=3.64, p=0.057) and a main effect of condition (F(1,7982)=19.89, p<0.0001). These main effects were qualified by an IAPS normative rating by condition interaction (F(1,7982)=6.8, p=0.0091). Follow up tests indicated that the effect of IAPS rating was significant in the experience condition (t(72)=3.2, p=0.0014, b=0.011) but not in the regulation condition (t(72)=-0.49, p=0.622, b=-0.0017) (Figure 6). These data indicate that pvmPFC activation tracts typical hedonic value during the basic experience of emotion, but not during emotion regulation.

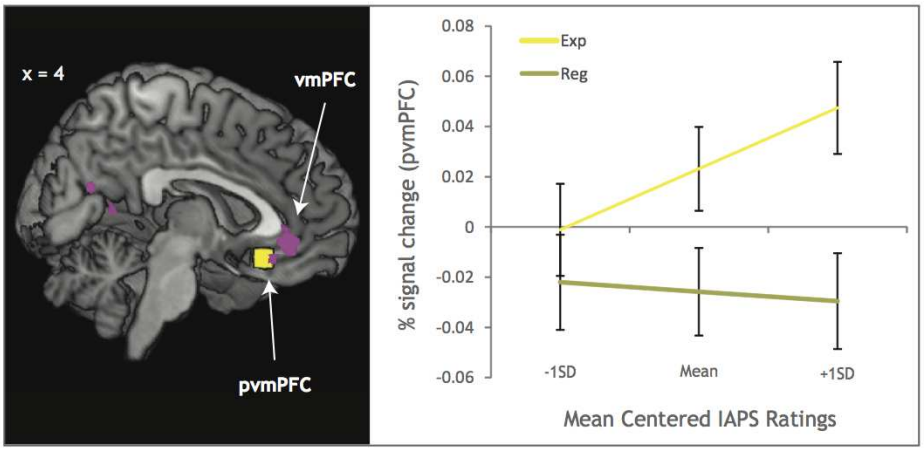

Figure 6: pvmPFC activation by normative IAPS Rating. (Left) Overlap between the vmPFC ROI from analysis 5b and pvmPFC ROI used to extract parameter estimates. (Right) Interaction plot for IAPS normative rating and condition on pvmPFC. Error bars reflect standard errors of the model predicted pvmPFC estimates. Within the Experience condition, IAPS normative rating predicted pvmPFC activation; however, there was no association with IAPS normative rating and pvmPFC activation during emotion regulation.

2.3.3 pvmPFC Activation and Differences in Behavioral Ratings

As a strong test for the role of pvmPFC in subjective emotional value, we next investigated whether pvmPFC activation predicted participants' trial-by-trial subjective ratings of each image. A GLM including experiment number, IAPS normative ratings, condition, the interaction of IAPS normative ratings and condition, and trial-by-trial estimates of pvmPFC activation significantly predicted behavioral ratings (full model: $F(5,8052)=2{,}370.75$, $p<0.0001$). The model revealed a main effect of normative IAPS rating ($F(1,8052)=13449.78$, $p<0.0001$, $b=0.37$) and a main effect of condition ($F(1,8052)=190.44$, $p<0.0001$, $b=0.026$); however, the main effects of normative IAPS ratings and condition

were qualified by a significant interaction ($F(1,8052)=1841.71$, $p<0.0001$, $b=0.433$). Additionally, there was a main effect of pvmPFC activation ($F(1,8052)=4.0$, $p=0.046$, $b=0.051$). These data indicate that even after accounting for the strong behavioral effects of our manipulation, pvmPFC activation still predicts the subjective experience of emotional value (Table 2).

Table 2: Effect of reappraisal, IAPS rating and pvmPFC activation on behavior. A general linear model revealed that IAPS normative rating, condition, and an IAPS normative rating by condition interaction predicted valence ratings. In addition, there was also a significant relationship between pvmPFC activation and behavior. [* denotes significance at $p<0.05$]

Variable	**Parameter Estimate (SE)**
Intercept	4.18 (0.047)*
Experiment	0.04 (0.026)
IAPS Rating	0.37 (0.008)*
Condition	0.31 (0.026)*
IAPS*Condition	0.43 (0.012)*
pvmPFC	0.05 (0.026)*
Overall Model	
R^2=0.06*	

2.4 Discussion

The vast majority of studies on the neural mechanisms of emotion regulation have focused on emotional reactions to negative stimuli. Though positive affect is beneficial for mental and physical health (Richman et al., 2005; Tugade, Fredrickson, & Barrett, 2004), not all of the consequences of positive affect are adaptive. When purchasing a new home, for example, the positive emotion induced by visualizing a

blooming garden in springtime could interfere with the negotiation of a better price. Unregulated positive affect increases distractibility in tasks that require cognitive control (Dreisbach & Goschke, 2004), inflates evaluations of the probability of winning in monetary gambling tasks (Nygren, Isen, Taylor, & Dulin, 1996), and increases the likelihood of impulsive purchasing decisions (Weinberg & Gottwald, 1982). In each case, a failure to regulate positive affect interferes with the attainment of goals.

Using stimuli falling along a continuous scale of emotional valence from positive to negative—and replication between two experiments—we show that a region within vmPFC tracks the subjective value of emotional stimuli. We also examined which sorts of affective processes are encoded by the vmPFC: normative stimulus valence (Lebreton, Jorge, Michel, Thirion, & Pessiglione, 2009), the engagement of goal-directed regulatory processes (Hare, Camerer, & Rangel, 2009), and/or trial-to-trial variation in subjective hedonic value across stimuli (Kable & Glimcher, 2007; Levy & Glimcher, 2011; Smith et al., 2010). Using an independently defined region of interest, we show that trial-to-trial variation in pvmPFC predicts the emotional hedonic value of affective images during the experience of emotion. These analyses converge on one common conclusion: In the context of emotion regulation, the vmPFC encodes stimulus-specific subjective hedonic value.

2.4.1 vmPFC: Common Economic and Emotional Value

Studies of reward processing have implicated the vmPFC in the valuation of rewards from various modalities: juice (Kim, Shimojo, & O'Doherty, 2006), faces (Lin, Adolphs, & Rangel, 2011; Smith et al., 2010), and non-monetary goods such as snack foods and CDs (Chib et al., 2009). This has led to the hypothesis that the vmPFC encodes a standardized value signal (Montague & Berns, 2002; Rangel & Hare, 2010). Though the common currency hypothesis rarely guides investigations of emotional processing, it can nonetheless account for vmPFC function in such studies. The vmPFC is engaged by a range of positive stimuli not typically characterized as rewards, including pleasant imagined stimuli (Cunningham et al., 2011) and happy memories (Lane et al., 1997). These studies support the idea that vmPFC computes a domain-general hedonic value signal (Roy, Shohamy, & Wager, 2012), manifest in our own data as emotional reward value. That is, positive emotion (like reward) is encoded along a continuous scale rather than as a binary signal of valence.

2.4.2 vmPFC: Cognitive Control or Domain-General Subjective Value?

Several lines of research have implicated the vmPFC as central to executing cognitive control. Studies of fear conditioning link vmPFC to the extinction of fear (Hartley & Phelps, 2010). Similarly, the reappraisal of negative emotion leads to activation in the vmPFC (Delgado, Nearing, Ledoux, & Phelps, 2008; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Urry et al., 2006). One investigation of

reappraisal of positive emotion demonstrated that increasing positive emotion also recruits the vmPFC (Kim & Hamann, 2007). These findings suggest that the vmPFC, like regions of the dlPFC also activated during emotion regulation (Ochsner & Gross, 2005), serves as a locus of affective control. Another interpretation is equally plausible, however: changes in vmPFC activation during regulation could reflect changes in the integrated hedonic value of emotional stimuli. Our own analyses are consistent with this conclusion.

Our results predict that while activation in the vmPFC reflects the subjective hedonic value of emotional stimuli after regulation has taken place, regions other than vmPFC will track the process of regulation itself. In one recent investigation (Hutcherson, Plassmann, Gross, & Rangel, 2012), food-deprived participants were prompted by a cue to down-regulate, experience, or up-regulate their affective responses to images of food items. Participants then indicated how much money they would be willing to pay for an opportunity to consume that item. During regulation there was a decrease in the association between vmPFC activation and monetary bids and a concurrent increase in the association between the dlPFC and monetary bids. Consistent with this result, we found greater signal in the dlPFC during the reappraisal of stimuli than during the experience of images even when they stimuli matched in subjective emotional value. That is, stimuli rated as neutral in the experience condition showed less activation in the dlPFC than stimuli rated as neutral in the regulation condition.

Furthermore, this relationship held for both positive and negative images. Compared to the regulation of positive images, the experience of neutral images activated regions previously linked to the emotional content of experienced stimuli.

Though in our study the dlPFC did not track hedonic value directly, dlPFC signal in the regulation condition might reflect computations that are ultimately integrated into the final encoding of value. That is, signal in the dlPFC may reflect conceptualization processes that are incorporated into subjective affective reactions. Participants in our regulation condition were asked to attempt to emotionally detach themselves from the images (i.e., to neutralize emotional responses). Though they were encouraged to report their emotional responses according to how they actually felt, it was clear that the ultimate goal of reappraisal was to alter their emotional experiences. Consequently, achieving the goal of regulation might contribute to an integrated neural signal for value.

This interpretation dovetails with findings from a study in which dieters rated both the tastiness and healthiness of food items in advance of making decisions about whether or not to consume those food items (Hare et al., 2009). Subjects who successfully implemented self-control evinced increased activation in the dlPFC (BA 9) and decreased activation in the vmPFC when deciding not to consume a tasty but unhealthy food – a result interpreted as evidence that the vmPFC integrates goal value as well as hedonic value. For both experimental samples in our study, we observed

regulation-related activation in the same dlPFC region that interacted with vmPFC in the connectivity analysis of Hare and colleagues. Thus, activation in the dlPFC during regulation could reflect the parametric contribution of regulation to the ultimate value of the stimulus, which is manifest in our data as decreased activation in the vmPFC.

In summary, our results indicate that the vmPFC does not act as a control region during emotion regulation but rather encodes the affective value of emotional stimuli along a continuous scale. From the perspective of a domain-general constructionist model of affect, the vmPFC encodes hedonic value across reward, emotion, and social processing; however, this encoding also reflects conceptualization processes. Conceptualization processes such as emotion regulation affect the hedonic value of stimuli as they are subjectively experienced. The vmPFC encodes this modified form of hedonic value rather than objectively encoding hedonic value irrespective of context. Much as emotional processes can be described as "situated in context" (Lindquist & Barrett, 2012), the encoding of hedonic value in the vmPFC can be thought of as situated within the broader array of psychological processes occurring during the experience of affective stimuli.

3. Domain-General Affective Disturbances in Anorexia Nervosa

In addition to positing shared neural mechanisms for core affect and conceptualization, a domain-general theory of affect makes important predictions about the nature of affective disturbances in psychiatric conditions. Many psychological disorders are characterized primarily by abnormalities in one particular affective domain. For example, it has been hypothesized that drug addiction results from pathological reward motivation (Kalivas & Volkow, 2005). In contrast, major depressive disorder (MDD) is thought to result from abnormal emotional experience and deficits in emotion regulation (Beauregard, Paquette, & Lévesque, 2006). Yet individuals with methamphetamine addiction experience profound social problems (Homer et al., 2008), and patients with MDD show changes in neural responses to monetary rewards (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). A domain-general theory of affect can help explain the heterogeneity of affective disturbances in psychiatric disorders and could potentially lead to novel insights into how psychiatric disorders develop and can be treated.

One disorder that could be better understood through the domain-general model of affect is anorexia nervosa (AN). Compared to other psychiatric conditions such as addiction and depression, the pathophysiology is AN is relatively poorly understood; This gap in knowledge is particularly compelling as the consequences of the disorder

can be dire. In one investigation, during the first year following a first-time admission to a hospital, patients with AN were nearly 20 times more likely to die of unnatural causes than the general population. Furthermore, this increased risk of death persisted over time, with patients showing an 8-fold increase in risk of death 20 years after their initial hospital admission (Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). Compounding the risk of mortality in AN, many who develop the disorder relapse (Pike, 1998) or experience ongoing subclinical problems (Wagner et al., 2006). Furthermore, treatment options, particularly for adults with AN, are limited (Agras et al., 2004). Given the severity of AN and the many impediments to full-recovery, it is critical to understand the factors that contribute to disordered eating.

A popular folk-psychological theory is that unreasonable standards of beauty promoted on television, in movies, and in magazines are adopted by women and girls, and their efforts to attain these standards ultimately cause anorexia. This theory is bolstered by evidence that prevalence rates of disordered eating and body image disturbances are higher in cultures with access to Western media (Makino, Tsuboi, & Dennerstein, 2004). However, while exposure to such images can have a deleterious effect on body self-esteem in some individuals (Ferguson, 2013; Roberts & Good, 2010), it fails to explain how in an environment saturated with images of unattainable beauty and thinness, only a small proportion of the general population ever meets full diagnostic criteria for AN. The etiology of AN is complex, and is likely the result of

interactions amongst genetic, neurobiological, and cultural factors (Bulik, 2005; Collier & Treasure, 2004; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Zucker et al., 2007). However, as the body of research on AN grows, numerous studies point to affective factors in the development and maintenance of disordered eating. Conceptualizing AN through the lens of a domain-general theory of affect could help elucidate some of the commonalities in abnormal processing and behavior across a range of circumstances.

3.1 Core Affective Disruptions in AN

In the constructionist model of emotion proposed by Lindquist, Barrett, and colleagues (Lindquist & Barrett, 2012), core affect is described as arising from fluctuations in the state of the body that are subjectively experienced as sensations containing both valence (i.e., hedonic value) and magnitude (i.e., arousal). Though findings on reward, emotion, and social processing in AN are varied, the overall corpus of literature suggests that a disruption in core affect is one key element of disordered eating.

3.1.1 Disruptions in Hedonic Value Processing

While more than 30% of U.S. adults are currently obese (Flegal, Carroll, Ogden, & Curtin, 2010), individuals with AN are able to resist consuming highly palatable foods (i.e., those high in fat and sugar). This feature of the disorder alone is suggestive of alterations in hedonic processing. That currently-ill patients with AN report preferring

high fat tastes less (Stoner, Fedoroff, Andersen, & Rolls, 1996; Sunday & Halmi, 1990), and that patients' aversion to high fat content does not resolve with treatment (Sunday & Halmi, 1990) suggests that people who develop anorexia have a fundamentally diminished response to hedonic stimuli. Regardless of whether these changes are hard-wired or occur because patients form negative associations between energy dense foods and weight gain, reward-related behaviors in AN are nonetheless transformed. Meta-analytic data examining self-report studies indicate that patients with AN demonstrate lower scores on the novelty seeking subscale of the Temperament and Character Inventory (Harrison, O'Brien, Lopez, & Treasure, 2010). Similarly, patients with restricting-type AN report reduced fun-seeking tendencies on the Behavioral Activation/Behavioral Inhibition System questionnaire (Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006). Moreover, women with AN report higher levels of social anhedonia (Tchanturia et al., 2012) and show lower levels of sexual drive (Castellini et al., 2012; Pinheiro et al., 2010). Beyond self-report data, one laboratory experiment indicated that patients with AN show less temporal discounting than healthy controls (Steinglass et al., 2012), and another demonstrated that weight-restored patients were less willing to sacrifice money to view social images (Watson, Werling, Zucker, & Platt, 2010).

Results across gustatory, monetary, and social domains imply that women with AN have reduced responsiveness to reward. Thus, one might infer that changes in

reward behavior in individuals with AN are driven by a *hyposensitive* reward system in the brain. Much of the neuroscientific data, however, seems to imply the opposite: that in patients with AN, the neural circuitry responsible reward processing is actually *hypersensitive*. The neurotransmitter dopamine has a well-characterized role in reward processing and motivation (Schultz, 2000). As a result, this neurotransmitter system has been the major focus of numerous studies of AN. In women recovered from anorexia, homovanillic acid (HVA), which is a dopamine metabolite, is less concentrated in the cerebrospinal fluid (CSF) than in control women (Kaye, Frank, & McConaha, 1999). Moreover, positron emission tomography (PET) research has shown that recovered participants demonstrate increased D2/D3 receptor binding in the ventral striatum (Frank et al., 2005), a region known to be involved in reward valuation (Knutson, Delgados, & Phillips, 2008). Because D2/D3 receptors perform different roles in different subregions of the ventral striatum (Besson et al., 2010), the interpretation of this finding in isolation is complex; however, looking across studies on dopamine processing in AN, it has been hypothesized that AN is associated with an increase in the density of D2/D3 receptors, a reduction in extracellular dopamine levels, or both (Kaye, Fudge, & Paulus, 2009).

Parkinson's patients with pathological gambling problems demonstrate lower D2/D3 binding both at baseline as well as during a gambling task (Steeves et al., 2009). Similarly, D2/D3 receptor availability in regular methamphetamine users is reduced in

the striatum, and reduced striatal D2/D3 receptor availability in these subjects is associated with increased impulsivity (Lee et al., 2009). Thus, whereas decreased binding of striatal dopamine receptors in addictive behaviors may relate to behavioral disinhibition and reward seekingness, increased D2/D3 binding in AN may result in the opposite—behavioral inhibition and reduced reward motivation. Supporting this conclusion, one recent fMRI study indicated that compared to healthy controls, women with AN showed greater response in the ventral striatum to unexpected pleasant tastes (i.e., larger prediction error). In contrast, compared to healthy controls, obese women showed reduced signal in the ventral striatum (Frank et al., 2012). These data suggest that reward hyposensitivity might drive over-consumption and food approach whereas reward hypersensitivity might drive under-consumption and food avoidance.

Though studies of reward function in AN are strongly suggestive of neurocircuit abnormalities, they do not necessarily account for how neural processing changes might drive food avoidance. One recent study, however, provides a potential explanation. Bailer and colleagues (2012) had recovered patients and healthy control women undergo PET scanning after receiving amphetamine administration. After a short delay, participants were then asked to rate aspects of their subjective emotional states. Though in control women D2/D3 binding potential in the ventral striatum was associated with an increase in happiness following drug administration, women with a history of AN showed no such effect. In contrast, women with AN showed an increase in reported

anxiety following drug administration, and this anxiety response was associated with an increase in D2/D3 binding potential in the dorsal caudate. This result fits with other data indicating that binding potential in the dorsal striatum in recovered women is positively associated with the personality trait of harm avoidance (Frank et al., 2005). Therefore, while activation of the reward system may be experienced as subjectively pleasurable in normal individuals, it may be subjectively aversive in women with AN, which could perpetuate an avoidance of stimuli that activate reward circuitry in the brain (e.g., food and social interaction).

Taken together, studies of reward processing in AN are suggestive of disturbances in how stimuli are assigned subjective hedonic value. Based on much of the available data on reward processing in AN, it is difficult to determine whether disturbances in reward processing occur in response to disruptions in neurobiological systems responsible for processing rewards, whether they occur in response to patients' desire to control motivational drives, or both. Though most studies document anhedonia in AN, some data indicate women with AN place positive value on exercise-related stimuli (Giel et al., 2013). This result, combined with the absence of differences between explicit preference ratings for low calorie foods (Stoner et al., 1996), might imply that the reward system in AN has been tuned to overvalue disorder-relevant goals and undervalue primary and social reinforcers. To explore this hypothesis, future studies should investigate whether neural reward response is increased when patients view

stimuli that are consistent with their weight-loss goals, and whether the class of stimuli that activate reward circuitry in AN changes as patients' weight and cognitive processing normalizes following treatment.

3.1.2 Disruptions in Punishment Processing

In addition to changes in positive hedonic valuation, it is probable that heightened negative hedonic valuation and arousal also play a role in the etiology of AN. One of the ways in which heightened negative affectivity is manifested in AN is in increased anxiety. Comorbidity studies consistently document high rates of anxiety disorders in patients with AN (Hudson, Hiripi, Pope, & Kessler, 2007; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004). In one study, nearly two thirds of a sample of women with AN had some form of concurrent anxiety disorder, with over 40 percent meeting criteria for obsessive compulsive disorder, 20 percent meeting criteria for social phobia, 15 percent meeting criteria for specific phobias, and others meeting criteria for generalized anxiety disorder, post-traumatic stress disorder, panic disorder, or agoraphobia (Kaye et al., 2004). This study is consistent with other data documenting the high levels of comorbidity with other affectively-related Axis I diagnoses in AN, such as major depression, specific phobia, and social phobia (Hudson et al., 2007). High levels of anxiety, particularly social anxiety, are reported prior to the onset of disordered eating (Kaye et al., 2004), and anxiety disorders are often present in first-degree relatives of those with AN (Strober, Freeman, Lampert, & Diamond, 2007). These data suggest that

increased negative affect is a trait feature of people who develop AN rather that a consequence of starvation. Treatment outcomes, therefore, could potentially be improved by understanding how negative affect contributes to disordered eating.

Beyond elevated rates of DSM diagnoses for anxiety disorders, women with AN also show increased negative affect in individual difference measures and laboratory tasks. For example, on the Temperament and Character Inventory (Cloninger, Svrakic, & Wetzel, 1994) women with AN score higher on the harm avoidance subscale (Harrison, O'Brien, et al., 2010), indicating that they show a tendency to excessively worry, mentally fatigue easily, fear uncertainty, and withdraw socially (Cloninger, Svrakic, & Przybeck, 1993). Paralleling these findings, women with AN demonstrate an attentional bias towards threatening faces (Harrison, Tchanturia, & Treasure, 2010) indicating hypervigilance to negative social cues. Similarly, looking across studies, women with AN demonstrate an increased Stroop effect for body and weight-related stimuli (Dobson & Dozois, 2004), which suggests that these stimuli may be treated by individuals with eating disorders in the same way that violent words and threat-related stimuli are processed by normal participants. This profile of state-level increases in anxiety and heightened sensitivity to potential threat suggests that women who go on to develop eating disorders may be prone to over-engage with negative cues in the environment.

In contrast to the neurotransmitter dopamine, which has been strongly implicated in reward learning, it has been hypothesized that serotonin (5-HT) may be

critical for learning from punishment (Boureau & Dayan, 2011). Moreover, individual differences in the temperament trait of harm avoidance are thought to be mediated through the serotonin system (Cloninger, 1987); therefore, serotonergic processing differences in AN may be responsible for the increase threat sensitivity. Beyond the affective function of serotonin, 5-HT is also involved in appetite regulation (Blundell & Halford, 1998). Thus, changes in serotonergic processing could potentially account for disturbances in both eating and aversive responses in AN (Kaye et al., 2009). To explore such changes, early studies examined CSF concentrations of 5-hydroxyindoleactice acid (5-HIAA), which is the major metabolite of 5-HT in the brain. Results indicated that when ill, women with AN show decreased accumulation of 5-HIAA in CSF (Kaye, Gwirtsman, George, Jimerson, & Ebert, 1988), but following weight restoration patients show no difference (Kaye et al., 1988; Kaye, Gwirtsman, Ebert, & Weiss, 1984) or even elevated levels of 5-HIAA (Kaye, Gwirtsman, George, & Ebert, 1991). These results suggest that extracellular levels of 5-HT, which are thought to correspond to 5-HIAA levels (Stanley, Traskman-Bendz, & Dorvonini-Zis, 1985), may vary depending the stage of the disorder and may drive behavioral changes accordingly. More recent investigations taking advantage of PET or single-photon emission computerized tomography (SPECT) have also found alterations in the 5-HT system in AN. Consistent with the hypothesis that currently-ill women with AN have reduced extracellular concentrations of 5-HT, one PET study found increased 5-HT_{1A} binding in regions of the

prefrontal, cingulate, and orbitofrontal cortex (Bailer, Frank, Henry, Price, Meltzer, Mathis, et al., 2007). A similar study investigating the 5-HT transporter found greater binding potential in women with AN in the ventral striatum (Bailer, Frank, Henry, Price, Meltzer, Becker, et al., 2007). In contrast, studies of 5-HT_{2A} have shown decreased binding in the left frontal cortex, bilateral parietal cortex, and bilateral occipital cortex during the ill state (Audenaert, Laere, Dumont, & Vervaet, 2003) and in the amygdala, hippocampus, and cingulate after recovery (Frank et al., 2002).

Pointing towards the affective consequences of altered 5-HT in AN, harm avoidance has been shown to correlate with binding potential of 5-HT_{1A} and 5-HT_{2A} in regions involved in emotional processing (Bailer et al., 2004, 2005; Bailer, Frank, Henry, Price, Meltzer, Mathis, et al., 2007). Drawing on such results, Kaye, Fudge & Paulus (2009) have hypothesized that individuals who will develop AN have altered extracellular serotonin paired with an imbalance between 5-HT_{1A} and 5-HT_{2A} receptor density, predisposing these individuals towards negative emotionality. As a consequence of social and hormonal changes occurring during puberty, further changes to the 5-HT system exacerbate disturbed mood and satiety processing, leading to increased dieting. Extreme dieting serves to reduce mood disturbance during the ill-state by reducing in 5-HIAA and increasing binding of 5-HT_{1A}. As 5-HT activity normalizes during weight restoration, however, patients experience dysregulated mood

and emotion, perpetuating the cycle of disturbed affect and attempts to control affect through disordered eating.

3.1.3 Disruptions in Bodily and Interoceptive Signal Processing

The corpus of existing research on reward and punishment sensitivity in AN suggest that key experiential elements of core affect are disrupted in AN. Yet, core affective properties are thought to originate from fluctuations in bodily sensations (Lindquist & Barrett, 2012; Lindquist et al., 2012). As a result, changes in the representation of bodily feedback should also have consequences for core affective responses. One of the diagnostic features of anorexia is a disturbance in the experience of the body. For example, and women with AN often overestimate the size of their own bodies (Skrzypek, Wehmeier, & Remschmidt, 2001) and demonstrate exceptionally poor body self-esteem (Cash & Brown, 1987). While these changes may be suggestive of a higher-order cognitive disturbance, the disruption in body experience may also occur at the level of basic somatic sensation and bottom-up interoceptive responses. Thus, how changes in the subjective experience of core affect arise may be dependent on alterations in the experiential accuracy, integration, and neural representation of bodily feedback in AN.

Though the majority of studies examining bodily disturbance in AN rely entirely on self-report questionnaires (e.g., Adenzato, Todisco, & Ardito, 2012; Simon Baron-Cohen et al., 2013; Merwin et al., 2013), a handful have probed patients' responses to

objectively quantifiable interoceptive signals or sensory stimulation. Using a task in which participants were asked to estimate the length between two tactile stimuli on the body, Keizer et al, (2011) demonstrated that currently-ill patients were less accurate at tactile perception than controls. Furthermore, the tendency to overestimate the size between two tactile stimuli was associated with greater body image disturbance in participants with AN. Previous research has demonstrated that tactile perception can be altered by manipulating participants' experience of their body (de Vignemont, Ehrsson, & Haggard, 2005; Ehrsson, Kito, Sadato, Passingham, & Naito, 2005; Taylor-Clarke, Jacobsen, & Haggard, 2004). Thus, it is unclear whether the difference in tactile estimation is due to changes in basic somatosensory perception or disorder-related alterations in the body experience.

To resolve this question, Keitzer and colleagues (2012) performed a follow up experiment using a pressure detection task and a two-point discrimination task, both tasks thought to measure basic tactile perception. They also used their previously employed tactile estimation task, which they hypothesized would be more sensitive to contextual manipulation. Group differences were observed in all three tasks. In the tactile discrimination task, patients required more distance than controls between the two stimulation points distinguish them. Replicating previous findings, patients also overestimated the distance between two points in the tactile estimation task. Interestingly, while there were no differences between force detection between patients

and controls when stimuli were applied to the arm, patients were able to detect stimuli at lower levels of force on the abdomen, implying that disturbances in somatic sensation may not be due entirely to reduced sensory perception, but may vary depending on how much attention a patient pays to a particular body area.

Paralleling differences in tactile perception, evidence suggests that patients with AN have altered interoceptive processing. To explore the nature of interoceptive changes in AN, Pollatos and colleagues (2008) had patients and control participants perform a heartbeat detection task. In addition to assessing objective interoceptive sensitivity, they also assessed subjective interoceptive perception through the interoceptive awareness scale portion of the Eating Disorders Inventory. Results indicated that patients were less accurate than controls on the heartbeat detection task and reported poorer interoceptive awareness. These results imply that patients with AN are less sensitive to signals arising from the body. Also pointing towards reduced visceral and somatosensory reactivity in AN, several studies have indicated that currently-ill patients demonstrate higher pain thresholds (Bär et al., 2006; Krieg, Roscher, Strian, Pirke, & Lautenbacher, 1993). Taken together, these results could suggest that individuals who develop AN are less sensitive to bodily sensations, a predisposition that might lead to inattention to hunger and fatigue.

This theory, however, ignores at least one important consideration with respect to clinical investigation, namely the problem of differentiating the chicken from the egg.

In the general population, only a relatively small proportion of people will develop the disorder (Hudson et al., 2007). Consequently, it is extremely difficult to perform prospective studies in participants who will develop AN. This creates a challenge in determining whether abnormalities that manifest during the acute phase of anorexia are a consequence of starvation or a cause. In contrast to the theory that *reduced* interoceptive processing may trigger disordered eating, others have hypothesized that *increased* interoceptive reactivity in combination with other factors may predispose certain individuals to developing AN (Kaye et al., 2009; Zucker et al., 2013). This hypothesis is supported by evidence that both currently-ill and weight-restored patients with AN report elevated sensory sensitivity (Merwin et al., 2013; Zucker et al., 2013). The conflict between these results and results suggesting that bodily sensitivity in AN is reduced (i.e., Keizer et al., 2011, 2012; Pollatos et al., 2008) may be due in part to changes in how core affective signals are treated by individuals with AN. Current and previous patients report greater sensory avoidance (Zucker et al., 2013) and emotional avoidance (Wildes, Ringham, & Marcus, 2010). Thus, chronically employed efforts to regulate and avoid bodily feedback might ultimately result in poorer ability to perceive and interpret such signals during the ill-state and possibly after recovery.

Given that visceral and somatic sensations are integral components of core affect, disturbances in bodily sensation perception in AN should be accompanied by changes in affective perception. Indeed, studies consistently show that patients with AN have high

levels of alexithymia, or difficulty identifying and describing feelings (for a review see (Nowakowski, McFarlane, & Cassin, 2013; but see Parling, Mortazavi, & Ghaderi, 2010). In addition to showing deficits in understanding their own sensations, feelings, and reactions, patients with AN also show a range of social cognitive deficits (Zucker et al., 2007), in particular in tasks that tap mentalizing and theory of mind skills (Harrison, Sullivan, Tchanturia, & Treasure, 2009; Oldershaw, Hambrook, Tchanturia, Treasure, & Schmidt, 2010; T. A. Russell, Schmidt, Doherty, Young, & Tchanturia, 2009; Tapajóz Pereira de Sampaio, Soneira, Aulicino, & Allegri, 2013). If models for how other people think and behave are built through simulation, as one prominent hypothesis for theory of mind would suggest (Gallese, Keysers, & Rizzolatti, 2004), it is intuitive that individuals with a limited capacity or willingness to process their own bodily and affective states would have difficulty understanding other people's emotions and social behavior. This could potentially explain the attachment difficulties patients with eating disorders often experience (Ward, Ramsay, Turnbull, Benedettini, & Treasure, 2000) and also the elevated levels of autistic traits in individuals with AN (Baron-Cohen et al., 2013; Hambrook, Tchanturia, Schmidt, Russell, & Treasure, 2008).

Dovetailing behavioral evidence on interoceptive and sensory dysfunction in AN, neuroimaging data support the idea that disturbances in somatic and visceral processing in AN are associated with altered reward, social, and affective functioning. A number of studies document changes in insular processing in anorexia (Table 3), leading

some to conclude that insular dysfunction is responsible for many of the behavioral disturbances in AN (Nunn, Frampton, Fuglset, Törzsök-Sonnevend, & Lask, 2011). While a few of these studies have found hypoactivation of the insula in AN (e.g., Wagner et al., 2007), a majority show increases in activation in the insula to disorder-relevant stimuli (Friederich et al., 2010; Miyake et al., 2012; Mohr et al., 2010; Oberndorfer, Frank, et al., 2013; Strigo et al., 2013). Whether disturbances in insula processing are specific to the more affectively-relevant anterior division (Chang et al., 2013) or the more somatosensory-relevant posterior insula (Chang et al., 2013) is unclear; however, an interaction between physical and affective disturbances may be at play. Notably, one study (Strigo et al., 2013) showed that while the anticipation of pain led to greater increases in anterior insula activation in women recovered from AN, pain stimulation led to less activation in the posterior insula in the clinical group. Thus, there may be a disconnect between the anticipation of physically or affectively aversive events in women with AN and their actual response to such events. The same study found that levels of alexithymia correlated with anterior insula activation during pain anticipation. Thus, the degree of the mismatch between expected and experienced responses may depend on an individual's ability to accurately perceive and describe sensations.

Table 3: Summary of neuroimaging findings on insular processing in AN

Paper	Task	Contrast	Laterality	Division
Bär et al., 2013	High pain vs. low pain stimulation	HC > AN	L	Posterior
Friederich et al., 2010	Thin body images	AN > HC	R	Anterior
Gizewski et al., 2010	Food vs. non-food images when sated	HC > AN AN > HC	R L	Posterior Posterior
Holsen et al., 2012	High calorie foods vs. objects before a meal High calorie foods vs. objects after a meal	HC > AN HC > AN HC > AN	B R L	Anterior Anterior Anterior
Miyake et al., 2012	Negative social words vs. control words	AN > HC	L	Posterior
Mohr et al., 2010	Compare thin body distortion to ideal body vs. compare thin body distortion to actual body	AN > HC	R	Anterior
Oberndorfer, Simmons, et al., 2013	Food vs. object images	REC > HC	R	Anterior
Oberndorfer, Frank, et al., 2013	Sucrose taste stimuli	HC > REC	R	Anterior (extending to posterior)
Redgrave et al., 2008	Stroop task for "Thin" vs. "XXXX"	AN > HC	L	Posterior
Sachdev, Mondraty, Wen, & Gulliford, 2008	Images of self vs. images of others	HC > AN	L	Anterior
Strigo et al., 2013	Pain anticipation Pain stimulation	REC > HC HC > REC	R R	Anterior Posterior
Wagner et al., 2007	Water and sucrose taste stimuli	HC > AN	B	ROI of entire insula

3.2 Conceptualization Disruptions in AN

In addition to disruptions in core affect, women with AN also show changes in how sensory and affective information is made meaningful. As construed by the constructionist model of emotion, affective responses are situated in context (Lindquist & Barrett, 2012). That is, the interpretation of an affective response is contingent upon prior associative learning, current goals, and current environment. A number of cognitive changes have been documented in AN including cognitive inflexibility (Tchanturia et al., 2004), a local versus global processing bias (Southgate, Tchanturia, & Treasure, 2008), and weak central coherence (Lopez, Tchanturia, Stahl, & Treasure, 2009). These cognitive changes no doubt contribute to how emotional and visceral stimuli are interpreted; however, changes in how consciously deployed emotion regulation is engaged also contributes to disruptions in AN. In contrast to other psychiatric disorders such as addiction, bipolar disorder, and depression, patients with AN are described as over-controlled expert emotion regulators relentlessly employing emotion regulation to attain weight-loss goals (Zucker & Harshaw, 2011). It is surprising, therefore, that the number of empirical studies specifically focused on emotion regulation in AN is limited (see Haynos & Fruzzetti, 2011 and Safer et al., 2011 for a discussion). Nonetheless, several experiments have taken advantage of the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) to assess emotion regulatory dysfunction in AN. The DERS is made up of six subscales focusing

on non-acceptance of emotional responses, difficulties engaging in goal-directed behavior in the face of negative emotion, problems with impulse control when experiencing emotions, problems accessing appropriate emotion regulation strategies when upset, lack of emotional clarity, and lack of emotional awareness. Differences in total DERS score (Harrison et al., 2009; Merwin et al., 2013) and all of the DERS subscales (Merwin et al., 2013) have been found between currently-ill patients and healthy controls. Though one study reported no differences between total DERS score between recovered patients and healthy controls (Harrison, Tchanturia, et al., 2010), another found differences in access to emotion regulation strategies, non-acceptance of emotional responses, emotional awareness, and emotional clarity (Merwin et al., 2013). Thus, problems with emotion regulation may be a predisposing factor for AN and may contribute to on-going disturbances following recovery.

One question given the limited ability to cope with emotional distress in patients with AN is how these individuals attempt to control emotional responses. Bradycardia is frequently observed during the ill-state (Halmi, 1974; Mont et al., 2003) as is hypothermia (Halmi, 1974), and a reduction in sympathetic nervous system responses to social stressors (Monteleone et al., 2011). These changes in physiological responses seem to be related to body weight. For example, self-reported interoceptive awareness and body mass index are inversely correlated (Pollatos et al., 2008). Similarly, currently-ill patients with lower BMIs report less emotion dysregulation (Brockmeyer et al., 2012);

thus, starvation itself may be a maladaptive strategy patients with AN employ to regulate hyper-reactive somatic sensations by turning down the gain on physiological responding altogether. In recovered patients, less emotion dysregulation is associated with less self-reported sensory sensitivity. As a result, recovery may be related to an improved ability to deal with uncomfortable bodily and affective sensations and to regulate them appropriately (Merwin et al., 2013).

In addition to employing starvation to control affect, there is evidence that women with AN attempt to regulate their emotions through maladaptive cognitive strategies. Patients with AN demonstrate blunted facial displays of emotion (Claes et al., 2012; Davies, Swan, Schmidt, & Tchanturia, 2012) despite stable (Davies et al., 2012) or elevated negative emotional experiences (Claes et al., 2012). These data suggest that patients with AN may over-engage in expressive suppression. That is, they attempt to control overt displays of emotion rather than trying to change the nature of their emotional experience through cognitive change (Gross & Thompson, 2007). As an emotion regulation strategy, expression suppression is suboptimal for at least two reasons. First, habitual use of expressive suppression, as compared to cognitive reappraisal, is associated with worse mental and social outcomes (John & Gross, 2004), and increased rather than decreased activation in the amygdala and insula (Goldin et al., 2008). Thus, this strategy likely increase rather than decreases negative emotionality and dysphoric mood typical of patients with AN. Second, emotions serve an important

function in signaling in social interactions. Blunted facial expressions of emotion in AN may interfere with clinicians' ability to form a therapeutic alliance with patients and could potentially contribute to day-to-day interpersonal difficulties (Zucker et al., 2007) and attachment problems associated with AN (Ward et al., 2000).

3.3 Summary of Affective Disruptions in AN

Both behavioral and neuroscience data suggests that AN is associated with disturbances in core affect as well as conceptualization. Consistent with the idea that reward, emotion, and social functioning rely on many common processes and neural circuits, these disruptions are not constrained to eating behaviors, but extend into emotional and social arenas. To that end, disruptions in core affect in AN result in reduced motivation to pursue rewards whether food, monetary, or social in nature and drive heightened harm avoidance across domains. Though the exact biological and psychological cause of these disruptions is not yet known, there is likely a role for altered processing of interoceptive and sensory stimuli in the insula, alterations in dopamine processing and reward circuitry, and changes in cognitive control implemented by the prefrontal and parietal cortices. Future research should investigate the degree to which disturbances in AN are domain general, and whether there are disruptions in AN that are specific to particular cognitive or affective processes.

4. Social Processing in Anorexia Nervosa is Associated with Disruptions in the Neural Mechanisms of Core Affect[1]

The body of evidence on anorexia nervosa (AN) indicates that patients experience disruptions in reward, emotional, and social processing. Taken collectively, prior studies suggest that there may be an overall skew in the processing of core affect, whereby patients with AN experience affective stimuli as aversive, irrespective of stimulus modality. Such a bias may be due to alterations in the experience of the body or interoceptive differences, functions that rely on the insular cortex. Here, we demonstrate that the neural circuitry involved in core affect (i.e., the insula) and conceptualization (i.e., the prefrontal cortex) are different in AN. Further, we show that eating disorder symptoms are related to changes in social anxiety.

4.1 Introduction

AN is a rare but serious psychiatric disorder that is associated with high rates of relapse (Richard, Bauer, & Kordy, 2005), suicidality (Bulik et al., 2008), and mortality (Birmingham, Su, Hlynsky, Goldner, & Gao, 2005). Though the primary diagnostic features of AN concern disturbances in eating, weight, and body experience (American Psychological Association, 2000), consistent with a domain-general theory of affect, patients with anorexia also display numerous disruptions in emotional and social

[1] This research was presented at the International Conference on Eating Disorders in May of 2013 and is co-authored by Karli Watson, Katie Gaddis, Lori Keeling, Michael Platt, Scott Huettel, and Nancy Zucker.

functioning (Zucker et al., 2007). For example, studies have indicated that women with AN show deficits in emotion recognition (Harrison et al., 2009; Oldershaw et al., 2010) and emotional empathy (Adenzato et al., 2012). Similarly, elevated levels of autism symptoms in AN have been reported in both adolescents (Baron-Cohen et al., 2013) as well as adults (Hambrook et al., 2008). In addition to socioemotional disturbances, women with AN show increased sensitivity to threat and punishment (Harrison, O'Brien, et al., 2010); therefore, one potential explanation for social dysfunction in AN is that social stimuli trigger aversive emotional responses, which promote social withdrawal and avoidance. This hypothesis is consistent with the elevated rates of social anxiety disorders in AN (Godart, Flament, Lecrubier, & Jeammet, 2000; Hinrichsen, Wright, Waller, & Meyer, 2003; Kaye et al., 2004) well as biases in visual attention towards angry (Harrison, Tchanturia, et al., 2010) and rejecting faces (Cardi, Di Matteo, Corfield, & Treasure, 2013).

Recent research has indicated that behavioral disturbances in AN are accompanied by neural changes in areas of the brain associated with affective processing (Phillipou, Rossell, & Castle, 2013). Though functional and structural differences have been observed in the amygdala (Holsen et al., 2012; Joos et al., 2011; Miyake et al., 2010) the cingulate cortex (Amianto et al., 2013; Cowdrey, Park, Harmer, & McCabe, 2011; Friederich et al., 2010; Joos et al., 2011) and the orbitofrontal cortex (Amianto et al., 2013; Frank et al., 2012; Frank, Shott, Hagman, & Yang, 2013), there has been a strong interest

in understanding how differences in insular functioning relate to symptoms in AN (Nunn et al., 2011). The insular cortex has been implicated in interoception, or representing the state of the body (Craig, 2009; Craig, 2002). Given the many interoceptive changes in AN (Pollatos et al., 2008; Zucker et al., 2013), it is understandable that patients demonstrate differential insular processing of food-related stimuli (e.g., Gizewski et al., 2010; Holsen et al., 2012; Oberndorfer, Frank, et al., 2013; Oberndorfer, Simmons, et al., 2013; Wagner et al., 2008). Yet, the insula has also been strongly implicated in a range of socioemotional processes such as responses to disgusting pictures (Britton et al., 2006), to over-priced goods (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007), and to social rejection (Eisenberger, Lieberman, & Williams, 2003). Consequently, if the encoding of affect is domain-general, we would expect patients with AN to demonstrate changes in insular engagement to food-related as well as socially-related stimuli.

Supporting this theory, one study by Miyake and colleagues (2012) showed that when women with AN were shown negative social words such as "betrayal" and "anger" they showed greater activation in the left posterior insula than when they viewed neutral words such as "movement" and "region." In another study of social processing in AN, patients showed greater activation in the right anterior insula when comparing their own body to an idealized thin body distortion (Friederich et al., 2010). While both of these studies point to increased insular processing of social stimuli in AN,

neither included an affectively neutral social condition as a control. As a result, it is not possible to determine whether the observed insular activation was related to the negative valence or the social nature of the stimuli. Further complicating the interpretation of insular changes in AN, several studies utilizing social stimuli have found no differences in insular activation in patients (Cowdrey, Harmer, Park, & McCabe, 2012; McAdams & Krawczyk, 2014).

In the current study, we sought to investigate the neural mechanisms of social processing in AN. To rule out the potential effects of starvation on brain response and cognition, our clinical population included subjects with a history of restricting-type anorexia, but who were currently weight restored. Subjects underwent functional magnetic resonance imaging (fMRI) while they viewed images of faces of varying attractiveness, bodies of varying weights, and scrambled images. In a separate testing session, participants rated the weight and attractiveness of each image they viewed in the scanner and also completed survey measures of social and emotional cognition. We hypothesized that when clinical participants viewed social images, they would show increased activation in the insular cortex and other affective regions, and that activation in these regions would be associated with increased social anxiety.

4.2 Materials and Methods

4.2.1 Participants

21 women with a history of anorexia (AN) and 23 healthy control (HC) women completed the experiment. Participants were recruited through fliers posted on the campuses of local universities and through a database of previous participants. All participants were first screened through a brief phone interview. Potential clinical participants then completed an online clinical duration interview, which was reviewed by a PhD-holding clinical psychologist to determine diagnosis. To be included in the sample, clinical participants had to have met DSM-IV criteria for restricting type AN in the past but have maintained a healthy weight for at least 6 months. Diagnoses based on the online interview data were again confirmed through an in-person structured clinical interview with a clinical psychology doctoral student with expertise in eating disorders. Participants who reported no history of disordered eating during the telephone screening were included in the healthy control sample and were selected to be matched to clinical participants on age, race, education, and medication status. Demographic characteristics of our sample are presented in Table 4.

Table 4: Demographic characteristics by group.

	HC **Mean (SD or %)**	**AN** **Mean (SD or %)**	***F***	***p***
Race				
• Caucasian	17 (73.9%)	16 (76.2%)	-	-
• Asian	3 (13.0%)	4 (19.0%)	-	-
• African American	2 (8.7%)	1 (4.8%)	-	-
• Native American	1 (4.3%)	0 (0.0%)	-	-

Age (years) Education (years)	25.13 (3.43) 15.72 (1.57)	22.48 (3.90) 15.86 (2.55)	6.20 0.05	0.02 0.83

4.2.2 Testing Procedure

All participants completed the experiment over the course of three or four testing days. Participants provided informed consent for a protocol approved by Duke University Medical Center's Institutional Review Board and were paid $30 per hour for their time. Prior to testing, participants completed an online battery of survey measures of emotional, interpersonal, and social functioning. On the first day of testing, participants completed consent and payment forms and were familiarized with the fMRI task inside a mock scanner, where they were also trained to minimize head movement. On the second day of testing participants underwent fMRI testing. For the last testing session, participants had the option of completing all of the remaining tasks over the course of one or two separate testing days. The final testing session included a battery of cognitive, social, and emotional tasks as well as the structured clinical interview. During this session, participants were shown all the images they viewed inside the scanner and were asked to rate the attractiveness of face and body images using a 9-point Likert scale from least attractive to most attractive. In addition, participants were asked to rate the weight of body images using a 9-point scale from extremely underweight to extremely overweight.

4.2.2.1 Survey Measures

To index current eating disorder symptoms, participants completed the Eating Disorders Examination Questionnaire (EDE-Q; Fairburn & Cooper, 1993). The EDE-Q is a 41-item survey that indexes both disordered eating behaviors as well as pathological cognitions about the body, food, and eating. Moreover, the survey asks about current height and weight allowing for the computation of body mass index (BMI). The EDE-Q has four subscales: restraint, eating concern, shape concern, and weight concern. A global EDE-Q score is calculated by averaging scores across the four subscales. In addition to indexing eating disorder symptoms, we also wanted to measure participants' level of social functioning. To do this, we had all participants also complete the Fear of Negative Evaluation questionnaire (FNE; Watson & Friend, 1969), which is composed of 30 true or false questions used to assess anxiety over negative social evaluation. Previous studies have documented that FNE is elevated in women with eating disorders (Hinrichsen et al., 2003), and that heightened FNE is associated with increased restrictive eating amongst non-clinical women (Gilbert & Meyer, 2005). Thus, we used scores on the FNE as an index of social anxiety and as a potential risk factor for ongoing disordered eating.

4.2.2.2 fMRI Stimuli

In our scanner task, participants were presented with 144 images each of female faces, female bodies, and scrambled face images. All images were drawn from publically

available Internet sources. Body images included the face and as well as the body from at least the waist up. Prior to our current study, a group of healthy female participants rated a large set of potential face and body images on weight and attractiveness. Images included in our current experimental protocol were selected based on these ratings to maximize variance in the weight and attractiveness dimensions.

4.2.2.3 fMRI Paradigm

The scanner task consisted of 6 functional runs with 72 trials each. Our task implemented a mixed blocked-event related design such that 8 images from each trial type (i.e., faces, bodies, scrambled) were presented consecutively. At the start of each trial an image from one of the image categories was presented onscreen for 2s. To ensure that participants were actively engaged in the task, on 12 trials per run participants were given 5s to rate the attractiveness of the image on a scale of one to four using a button box (Figure 7). Presentation order was pseudorandomized such that one of 10 timing templates designed to maximize model efficiency was selected from a randomized list. Inter-trial intervals were drawn from an exponential distribution with a minimum of 2s and a maximum of 12s. Images were displayed using Presentation software.

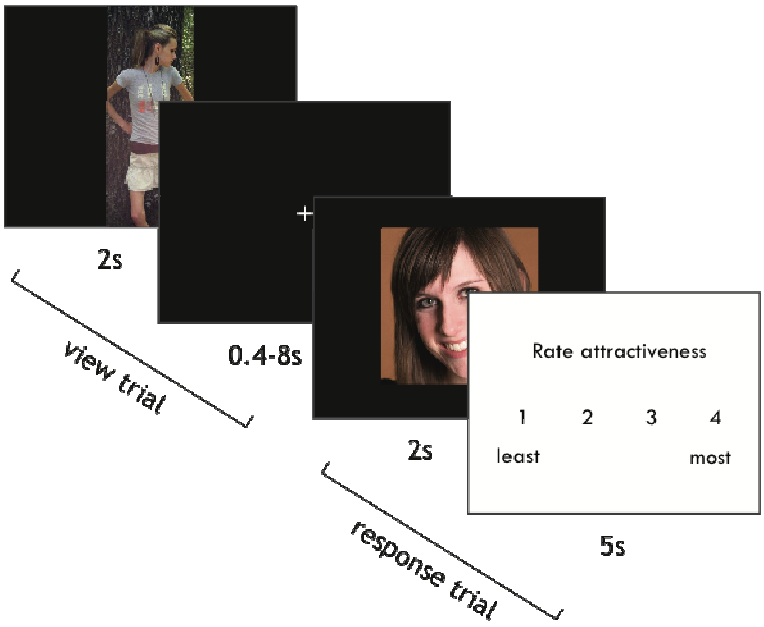

Figure 7: fMRI Task Paradigm. Participants viewed images of faces, bodies, and scrambled images for 2s. On most trials, image presentation was followed by a variable length inter-trial interval. On a subset of trials, participants were given 5s to rate the attractiveness of each image using a button box.

4.2.3 fMRI Acquisition & Preprocessing

Magnetic resonance images were acquired on a General Electric 3T scanner using a spiral-in pulse sequence. We utilized standard imaging parameters (TR=2s, TE=27ms FOV= 256mm, flip angle =60°, voxel size=4 x 4 x 4 mm, 20 axial slices collected parallel to the AC-PC plane). To allow for the stabilization of the fMRI signal, the first 5 volumes of each run were discarded. Due to a programming error, runs for the first ten participants contained variable numbers of volumes from 250 to 294. Data acquired for the rest of the participants contained 278 volumes of functional data per run. High-resolution

inversion-recovery prepared SPGR structural images were collected for each participant to aid in anatomical registration and normalization (TR=7.2ms, TE=2.9ms, FOV= 256mm, flip angle =12°, voxel size=1 x 1 x 1mm).

Preprocessing steps included brain extraction using BET, a high pass filter (>100s), spatial smoothing using a 6mm full-width half maximum Gaussian kernel, and motion correction using MCFLIRT. Motion correction occurred with respect to the middle volume of each run. FMRI data were normalized using transforms from each participant's own high resolution anatomical scan (6 degrees of freedom) and a Montreal Neurological Institute (MNI) anatomical template (12 degrees of freedom) using FLIRT.

4.2.4 fMRI & Behavioral Analysis

Behavioral data were analyzed using SAS Version 9.3. Analysis of FNE and EDE-Q scores was performed using a general linear model including group status as the independent variable. All EDE-Q subscale scores were analyzed separately. Weight and attractiveness ratings were analyzed using a multi-level model including participant as a random effect and group as a fixed effect. A restricted maximum likelihood estimation method and a variance components covariance structure were used. All reported statistics represent Type-III sums of squares.

Imaging data were analyzed using a general linear model in FSL version 4.1.8, FEAT version 5.98 (Smith et al., 2004). First-level models included regressors for each of

our image types (i.e., faces, bodies, scrambled images) and were corrected for local autocorrelation within a single run (Woolrich, Ripley, Brady, & Smith, 2001). At the second level, a fixed-effects model was used to combine data from all runs within a single participant. At the third level, a mixed-effects model was used to combine data across participants. For region of interest analyses, mean percent signal change was extracted from functional regions of interest using featquery.

To test for the basic effects of our manipulation, we created one regressor for each trial-type for the 2s presentation period as well as a nuisance regressor for the response period during trials in which participants made an attractiveness rating. We convolved all regressors with a standard double-gamma hemodynamic response function. We also tested for the effects of individual difference measures on patterns of neural activation by creating two separate models using participants' global scores on the EDE-Q and the FNE as a regressor at the third level. To isolate activation that specifically correlated with our individual differences measures, FNE and EDE-Q scores were orthogonalized with respect to the mean. All brain figures were produced using MRIcron (Rorden et al., 2007).

Due to a problem with the output files generated during the fMRI task, functional imaging data from one participant in the AN group was discarded. Out of the behavioral metrics, one control participant did not complete the EDE-Q. A total of 40 participants completed the FNE (21 AN, 19 HC), 20 clinical participants and 17 control

participants completed the attractiveness ratings task, and 17 clinical participants and 18 control participants completed the weight ratings task.

4.3 Results

4.3.1 Behavioral Results

Significant group differences emerged in the EDE-Q, with clinical participants showing elevated eating disorder symptoms in each of the four EDE-Q subscales as well as in the global EDE-Q (all *p*s<0.01). Similarly, though clinical participants were not currently underweight, they did show significantly lower BMIs than controls ((*F*(1,42)=4.6; *p*=0.038; Table 5). In addition to elevated eating disorder symptoms, analysis of FNE data indicated that participants with a history of AN also reported significantly greater fear of negative evaluation than controls (*F*(1,39)=7.31, *p*=0.01; Table 5).

Table 5: Fear of Negative Evaluation (FNE) and Eating Disorder Examination Questionnaire (EDE-Q) scores by group.

	HC Mean (SD)	**AN Mean (SD)**	***F***	***p***
EDE-Q				
• Current BMI	23.14 (7.44)	20.86 (8.2)	4.60	0.04
• Restraint	0.47 (0.70)	1.33 (0.98)	11.06	<0.01
• Eating Concern	0.08 (0.16)	0.72 (0.75)	15.85	<0.01
• Weight Concern	0.34 (0.41)	0.99 (0.95)	9.45	<0.01
• Shape Concern	0.67 (0.61)	1.88 (1.51)	11.87	<0.01
• Global	0.39 (0.41)	1.24 (0.95)	14.91	<0.01
FNE	8.90 (7.44)	15.52 (8.2)	7.31	0.01

To explore whether there was an association between eating disorder symptoms and social anxiety symptoms, we created a model in which clinical status, FNE score, and their interaction were included as independent variables and global EDE-Q was included as a dependent variable. Results indicated that FNE significantly predicted EDE-Q scores ($F(3,36)=4.77$; $p=0.036$) whereas neither group ($F(3,36)=0.71$; $p=0.40$) nor the group by FNE score interaction ($F(3,36)=1.40$; $p=0.24$) was significantly associated with global EDE-Q. Thus, social anxiety predicted disordered eating even when accounting for clinical status. No group differences emerged in attractiveness or weight ratings (Table 6). Thus, despite differences in social anxiety and disordered eating, explicit reports of the value of social images were not different for clinical participants.

Table 6: Attractiveness and weight ratings by group.

	HC Mean (SD)	**AN Mean (SD)**	***F***	***p***
Weight Ratings				
Bodies	4.71 (2.20)	4.84 (2.23)	0.81	0.38
Attractiveness Ratings				
Faces	5.08 (1.37)	4.89 (1.42)	0.81	0.37
Bodies	4.49 (2.06)	4.66 (2.27)	0.60	0.44

4.3.2 fMRI Results

In our fMRI analysis, results from the basic contrasts indicated that in response to body images, healthy control women showed greater activation in the middle frontal

gyrus (Max *Z*=4.36, *x*=46, *y*=20, *z*=40) while clinical participants showed greater activation in the lateral occipital cortex/occipital fusiform gyurs (Max *Z*=3.42, *x*=-30, *y*=-90, *z*=-20; Table 7). No group differences emerged for the contrast of face images.

Table 7: Group differences in whole-brain activation to body images.

Anatomical Label	*x,y,z*	Max *Z*
HC > AN		
middle frontal gyrus	46, 20, 40	4.36
AN > HC		
lateral occipital cortex/ occipital fusiform gyrus	-30, -90,-20	3.42

Beyond basic group differences, our parametric models revealed several neural changes associated with disordered eating and social cognition. The third-level analysis of current eating disorder symptoms across participants indicated that higher global scores on the EDE-Q were associated with stronger response in the right insula to faces (Max *Z*=3.71, *x*=40, *y*=11, *z*=-5, $p<0.001$, uncorrected; Table 8, Figure 8). Furthermore, participants with lower FNE scores showed increased activation in Heschl's gyrus and in the frontopolar cortex (Table 8, Figure 9).

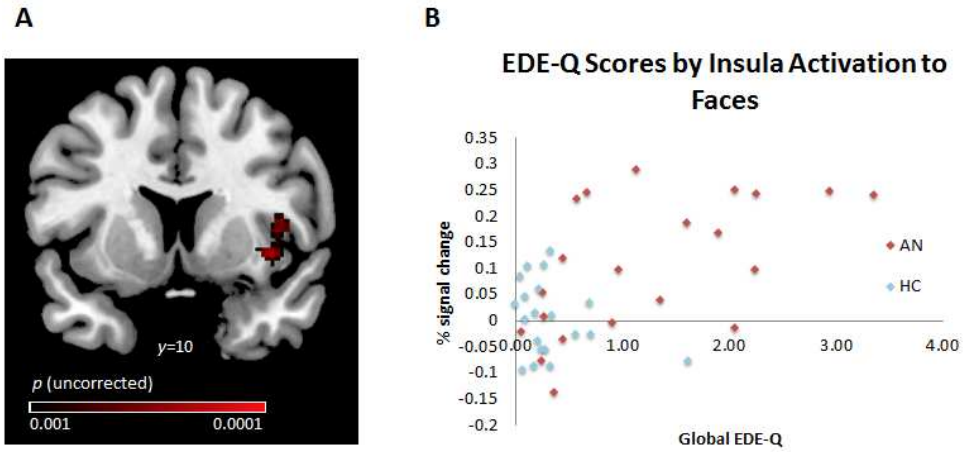

Figure 8: Whole-brain correlation with global Eating Disorder Examination Questionnaire (EDE-Q) scores. (A) Higher activation in the insula to face images is associated with higher global EDE-Q. (B) Scatter plot of mean % signal change in the insula by global EDE-Q by group.

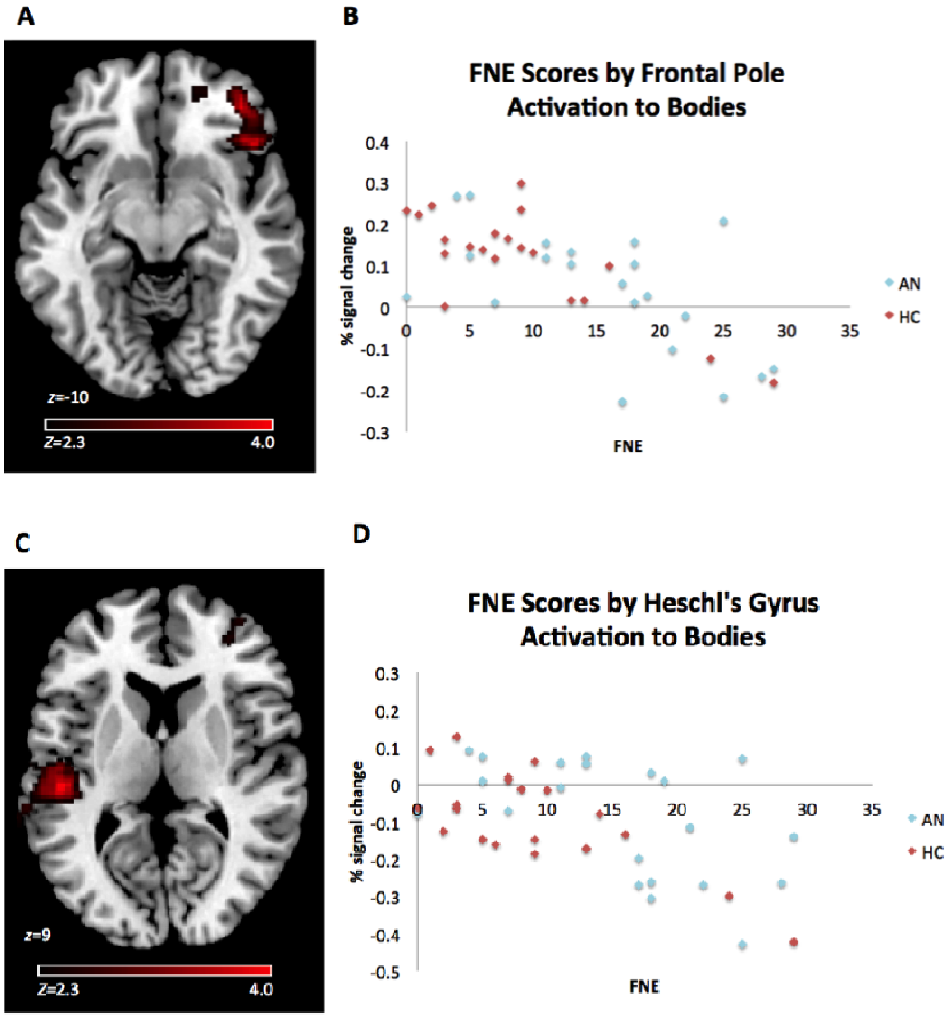

Figure 9: Whole brain correlations with Fear of Negative Evaluation (FNE) Scores. (A) Higher activation in the frontal pole to bodies is correlated with lower FNE. (B) Scatter plot of mean % signal change in the frontal pole and FNE by group. (C) Higher activation in Heschl's gyrus is correlated with lower FNE. (D) Scatter plot of mean % signal change in Heschl's gyrus and FNE scores by group.

Table 8: Correlation between brain activation and individual different factors

Anatomical Label	*x,y,z*	Max *Z*
Increasing EDE-Q & Face Images		
Insula	40, 11, -5	3.71
Increasing FNE & Bodies		
Frontal pole	44, 36, -20	4.07
Heschl's gyrus	-48, -26, 10	4.02

4.4 Discussion

Though extreme caloric restriction is itself associated with social withdrawal (Keys, Brozek, Henschel, Mickelson, & Taylor, 1950), there is evidence suggesting that interpersonal difficulties may be a predisposing factor in AN. Premorbid Asperger's syndrome, autism-like traits, and problems with social interaction have been reported (Gillberg & Råstam, 1992) as has premorbid social phobia (Kaye et al., 2004). These disruptions in social functioning often persist after recovery and contribute to ongoing psychological difficulties. At a ten-year follow up, problems with psychosocial functioning still affected nearly half of a sample of women with AN (Wentz, Gillberg, Gillberg, & Råstam, 2001), and 18% of these patients met diagnostic criteria for some variant of autism spectrum disorder at reassessment (Nilsson, Gillberg, Gillberg, & Råstam, 1999). Furthermore, the patients in this sample meeting criteria for a disorder involving social difficulties (autism spectrum disorder, obsessive-compulsive disorder, or obsessive-compulsive personality disorder) had particularly bad clinical, sexual, and

socioeconomic outcomes (Nilsson, Gillberg, Gillberg, & Råstam, 1999). Collectively, these results strongly signal a need to understand the relationship between social functioning and psychopathology in AN.

A domain-general theory of affect predicts that affective functions rely on common neural mechanisms. Thus, examining the neural mechanisms associated with core affect and conceptualization should lead to insight into the nature of social dysfunction in AN. Our results indicated that though participants with a history of AN did not differ in explicit ratings of the weight and attractiveness of social images, they did show a number of behavioral and neural changes associated with social processing. First, we found that our weight-restored participants reported higher levels of eating disorder symptoms in each of the EDE-Q subscales, suggesting they still experience cognitive and behavioral problems with eating. Consistent with a domain-general theory of affect, these participants also experienced greater fear of negative evaluation, indicating that ongoing disturbances were not constrained to eating-related behaviors, but also influenced socioemotional functioning.

Results from our fMRI analysis indicated that healthy control women showed greater activation in the middle frontal gyrus. This region of the brain has been frequently implicated in processes such as working memory (Owen, McMillan, Laird, & Bullmore, 2005), response inhibition (Blasi et al., 2006), reasoning (Krawczyk, Michelle McClelland, & Donovan, 2011), and emotion regulation (Winecoff et al., 2011). In

contrast, while viewing bodies, women with a history of AN showed greater activation in the lateral occipital gyrus extending into the lateral fusiform gyrus. These brain regions are involved in visual functions such as object processing (Hocking & Price, 2008) and attention to color (Barrett et al., 2001). Thus, it is possible that when viewing bodies, women with AN engage in primarily perceptual processing, which supports bottom up core affective responses, whereas healthy women engage more cognitive processes to conceptualize the meaning of these images in context.

In addition to basic group differences, we also found neural associations with individual differences in psychopathology. Across all participants, scores on the global EDE-Q correlated with activation in a sub-region of the insula during the presentation of faces. This aspect of the insula has been associated with painful heat (Farrell, Laird, & Egan, 2005) and mechanical stimulation (Maihöfner, Seifert, & Decol, 2011). Furthermore, studies informing participants that fear-evocative stimuli such as loud noises, shocks, or painful pressure will follow a particular cue (i.e., instructed fear) show consistent activation in this brain area (Mechias, Etkin, & Kalisch, 2010). Yet the role of this region is not constrained to somatic sensation alone. Highly empathic individuals showed increased activation in this area of the insula when witnessing social exclusion (Masten, Morelli, & Eisenberger, 2011). Thus, the insular region observed in our study seems to code for viscerally-evocative stimuli whether physical, emotional, or social.

In keeping with this hypothesis, there is evidence to suggest that differential insula processing in women with AN is associated with both changes in somatic sensation as well as emotional functioning. In a task in which participants anticipated and experienced painful heat stimulation, women recovered from AN showed a greater activation in an area of the insula just dorsal to our own brain-behavior correlation (Strigo et al., 2013). Furthermore, in this study, levels of alexithymia correlated with greater insular activation during pain anticipation in recovered anorexics. Thus, in individuals with high levels of current eating disorder symptoms, social stimuli may engage circuitry involved in the anticipation of threat. If social stimuli are experienced as subjectively threatening in these individuals, this response could further perpetuate interpersonal problems. Given the relationship between activation in the insula to pain anticipation and levels of alexithymia, this bias in associating bodily arousal with threat may be due to an inability or willingness to correctly interpret the visceral sensations activated by social stimuli.

In contrast to eating disorder symptoms, participants' anxiety about negative evaluation did not scale with activation in the insula or other regions of the brain frequently implicated threat or anxiety responses. FNE scored did, however, correlate with activation in the temporal lobe and in the frontopolar cortex. Given the role of the frontopolar cortex in self-referential processing (Sajonz et al., 2010), it is plausible that

participants with high levels of anxiety about social evaluation lack the ability to draw on knowledge about themselves to create accurate self-representations.

Taken together, our results indicate that even after weight restoration, eating and social disturbances in AN persist. Considered from the perspective of a domain-general theory of affect, the neural mechanisms of bodily signaling are overactive in individuals with AN. Given the bias towards negative affect in patients, these bodily responses may be interpreted as aversive, resulting in avoidance and withdrawal, not only from food, but also from social situations.

5. Disruptions in Core Affect Explain Social Dysfunction in Anorexia Nervosa

Results from previous neuroimaging studies as well as from Chapter 4 suggest that the neural mechanisms responsible for core affect are altered in individuals with anorexia nervosa (AN), and that these alterations may contribute to social deficits. In particular, changes in the insula, which is implicated in representing the affective and homeostatic state of the body, may lead to social dysfunction in AN. Given the insula's role in responses to threatening or painful stimuli (Mechias et al., 2010), one possible explanation is that individuals with disordered eating experience social stimuli as subjectively threatening. Here, we tested the hypothesis that social difficulties in AN are a consequence of biases in core affect and demonstrate that sensitivity to harm accounts for the association between disordered eating and social problems.

5.1 Introduction

Prior literature demonstrates that individuals with AN experience an overall increase in negative affect. For example, patients with AN show heightened anxiety (Godart, Flament, Lecrubier, & Jeammet, 2000; Kaye et al., 2004), higher levels of anger (Krug et al., 2008; Miotto, Pollini, Restaneo, Favaretto, & Preti, 2008), greater disgust sensitivity (Aharoni & Hertz, 2012), and high levels of harm avoidance (Fassino et al., 2002; Klump et al., 2004; Klump et al., 2000). In line with these findings, neuroscientific investigations of AN have revealed differential functioning in regions of the brain

responsible for processing arousal, emotion, and interoceptive stimuli (Kaye et al., 2009, 2013; Nunn, Frampton, Fuglset, Törzsök-Sonnevend, & Lask, 2011; Seeger, Braus, Ruf, Goldberger, & Schmidt, 2002).

The domain-general account of affect posits that disruptions to affective processing will affect not only bodily and emotional responses, but also social functioning. Evidence from animal studies supports this conclusion and has interesting implications for AN. In rats, exposure to a single series of foot shocks results in social withdrawal that persists for weeks (Mikics et al., 2008). Furthermore, social dysfunction itself may maintain affective disturbances. For example, following exposure to a socially-defeating interaction, rats show an initial decrease in body weight and an increase in anhedonia and defensive behaviors (Razzoli, Carboni, & Arban, 2009). Thus, increased threat sensitivity in AN may create a maladaptive cycle whereby patients experience their environment as threatening and avoid social interactions. When they do engage in interpersonal interactions, these interactions are judged as aversive, thereby perpetuating heightened anxiety and further social avoidance.

An affective profile in which social stimuli are associated with aversive responses could potentially explain the marked interpersonal problems individuals with AN experience. To examine the relationship between pathological eating, affective processing, and social dysfucntion, we had women with a current diagnosis of AN (AN), women with a prior diagnosis of AN but who were currently weight restored

(WR) and healthy control women (HC) complete survey measures to index their current eating disorder symptoms, personality, and social functioning. We hypothesized that women with current or previous AN would show heightened harm avoidance and reduced novelty seeking as indexed by the Temperament and Character Inventory. Moreover, we predicted that variability in these measures would predict poorer social functioning, particularly in clinical participants.

5.2 Materials and Methods

5.2.1 Participants

The experimental sample was made up of 52 female participants between the ages of 18 and 55 (*M*=27 years; SD=9.2 years). Participants were recruited through fliers posted at nearby universities, via online advertisements for websites focused on eating disorders, and through notices sent to mailing lists for local healthcare providers who specialize in eating disorders. To determine the clinical status of potential participants, all participants first completed a brief phone screening. Participants in the final sample also completed surveys to index lifetime eating disorder symptoms as well as an in-person structured clinical diagnostic interview conducted by a PhD-level clinical psychologist. To be included in the current AN sample (*n*=18), participants had to meet the criteria for AN as specified by the DSM-IV (American Psychiatric Association, 2000). Diverging from the DSM-IV criteria, however, in the current study participants were still eligible for inclusion in the AN sample if menstruation was present. For inclusion in the

WR sample (*n*=17) participants had to have previously met diagnostic criteria for AN but have been weight restored for at least six months. All participants included in the HC sample (*n*=20) had to have no current or previous eating disorder symptoms. Demographics characteristics of our sample are presented in Table 9. The majority of our sample was Caucasian and our participants were an average of 28 years old with an average of roughly an undergraduate education. Our groups did not differ significantly on education ($F(2,48)=1.75$, $p=0.219$).

Table 9: Demographics by Means (SD) or Frequency (%)

	AN (*n*=17)	**WR** (*n*=17)	**HC** (*n*=18)	**Total** (*n*=52)
Age	28 (9.41)	29 (10.49)	28 (10.33)	28 (9.9)
Years Education	15.06 (2.30)	16.75 (3.34)	15.78 (2.56)	15.84 (2.78)
Race/Ethnicity				
• White/Caucasian	18 (100%)	15 (88.2%)	10 (55.6%)	43 (83.0%)
• Black/African American	0 (0%)	1 (5.9%)	4 (22.2%)	5 (9.6%)
• Asian	0 (0%)	1 (5.9%)	1 (5.6%)	2 (4.0%)
• Hispanic/Latino	0 (0%)	0 (0%)	2 (11.1%)	2 (4.0%)
• Mixed Race	0 (0%)	0 (0%)	1 (5.6%)	1 (1.9%)
Relationship Status				
• Married	2 (11.8%)	5 (29.4%)	4 (22.2%)	11 (21.0%)
• Divorced	1 (5.9%)	0 (0%)	0 (0%)	1 (1.9%)
• Separated	1 (5.9%)	0 (0%)	0 (0%)	1 (1.9%)
• Engaged	0 (0%)	1 (5.9%)	0 (0%)	1 (1.9%)
• Single, Partnered	3 (17.6%)	4 (23.5%)	8 (44.4%)	15 (28.9%)
• Single, Not Partnered	10 (58.8%)	7 (41.2%)	6 (33.3%)	23 (44.2%)

5.2.2 Testing Procedure

Participants underwent a structured clinical interview and completed a battery of questionnaires to index cognitive, social, and emotional functioning as well as current and past eating disorder symptoms. Testing sessions were constrained to 3 hours, and participants were offered frequent breaks to avoid mental fatigue. For the current study, we only report results from the following subset of questionnaires drawn from the full experiment: Autism Spectrum Quotient, Eating Disorder Examination Questionnaire, and the Temperament and Character Inventory. Results from other questionnaires administered as a part of this study are reported elsewhere (Merwin et al., 2013; Zucker et al., 2013; Zucker et al., 2013).

5.2.2.1 Survey Measures

Autism Spectrum Quotient (*AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001)*. The AQ is a 50-item scale used to assess the level of autism-like traits in individuals with normal intelligence. Respondents indicate their answers to each item using a 4-point Likert scale, with higher scores reflecting more autism-like symptoms. Mean AQ scores for women have been reported as 15.4 (SD=5.7) for healthy control women and 38.1 (SD=4.4) for women with Asperger syndrome or high functioning autism (Baron-Cohen et al., 2001). Studies using both adults (Hambrook et al., 2008) and adolescents (Baron-Cohen et al., 2013) indicate that women with AN show elevated scores on the AQ compared to controls (adults with AN, *M*=23.2; adolescents with AN,

M=21.8). Based on Baron-Cohen and colleagues initial validation of the AQ, the original instrument was broken into five domains: social skills, attention switching, attention to detail, communication, and imagination (Baron-Cohen et al., 2001); however, a factor analysis of a large data set suggested that a three-factor structure including social skills deficits, details and pattern processing, and communication and mindreading deficits may be more appropriate (Austin, 2005). As a result, we utilized the three-factor model for our own analyses.

Eating Disorders Examination Questionnaire (*EDE-Q; Fairburn & Cooper, 1993)*. The EDE-Q is a brief, 41-item questionnaire used to assess current eating disorder symptoms both in terms of behavior and cognition. The scale first prompts respondents to report events that occurred in the past 28 days to orient them to the time period. For eating disordered behaviors, the questionnaire probes for the absence or presence of eating disorder symptoms within the previous 28 days and assesses frequency of occurrence either in total number of days the symptom was present (e.g., no days, 13-15 days, etc.) or number of times the symptoms occurred. For eating disorder cognitions, symptoms are assessed for the severity of respondents' concerns along a 7-point scale. For example, in response to "how dissatisfied have you been with your shape?" participants can respond from "0-not at all" to "6-markedly." The EDE-Q is composed of four subscales: restraint, eating concern, shape concern, and weight concern. A global EDE-Q score is computed by averaging scores across the four subscales.

Temperament and Character Inventory (*TCI; Cloninger, Svrakic, & Wetzel, 1994).* The TCI is a 240-item self-report scale used to assess aspects of personality and temperament. The TCI is broken into seven subscales, four measuring temperament (harm avoidance, novelty seeking, reward dependence, and persistence) and three measuring character (self-directedness, self-transcendence, and cooperativeness). Prior studies have indicated that as compared to healthy controls, patients with AN are typically high in harm avoidance (Fassino et al., 2002; Klump et al., 2000) and persistence (Fassino et al., 2002) and low in novelty seeking (Harrison, O'Brien, Lopez, & Treasure, 2010b; Klump et al., 2000), cooperativeness (Klump et al., 2000), and self-directedness (Fassino et al., 2002; Klump et al., 2004; Klump et al., 2000).

5.2.3 Data Analysis

All experimental variables were visually inspected, and measures for skewness and kurtosis were calculated to ensure a reasonable approximation of the normal distribution. For each outcome variable, observations that fell more than three standard deviations away from the mean were removed. After the removal of 2 observations (both HC) for cooperativeness scores and one observation (HC) for reward dependence on the TCI, all outcome variables demonstrated skewness and kurtosis values $< |2|$. Where participants failed to fill out all items of a questionnaire subscale or report information on any outcome measure, those participants' scores were removed from

analysis of those measures. Reported statistics represent values after the removal of incomplete data and outliers.

To test for group differences, we used SAS 9.3 to perform an ordinary least squares ANOVA including a three-level variable for group (i.e., AN, WR, HC) as our allowed-for factor. Where the overall model was significant, four follow-up contrasts were performed to indicate where groups differed (AN vs. HC, AN vs. WR, WR vs. HC, (AN+WR) vs. HC). Based on prior literature demonstrating differences in novelty seeking (Harrison, O'Brien, et al., 2010; Klump et al., 2000) and harm avoidance in AN (Fassino et al., 2002; Klump et al., 2004; Klump et al., 2000), we also performed two-step hierarchical regressions to explore whether novelty seeking or harm avoidance scores significantly improved estimates of participants' AQ social skills scores above and beyond group membership alone. At Step 1, we created a dummy variable for clinical status where healthy control participants were assigned a value of "0" and currently ill and recovered participants were assigned a value of "1." At Step 2, the regression included both the dummy variable for clinical status as well as scores on the harm avoidance and/or novelty seeking subscales of the TCI.

To examine whether the relationship between current eating disorder symptoms and social skills deficits could be explained by differences in either harm avoidance (*Mediation Model 1*) or novelty seeking (*Mediation Model 2*), we utilized the MBESS package developed for R to estimate 95% confidence intervals (Kelley, 2010; Kelley,

2007a, 2007b; Preacher & Kelley, 2011). A non-parametric bootstrap analysis with 10,000 samples was performed, and significance was determined based on whether the bootstrapped confidence interval contained 0 (Preacher & Hayes, 2004).

5.3 Results

5.3.1 Group Differences in Disordered Eating, Temperament, and Social Functioning

By design, there was an effect of group membership on current body mass index (BMI) ($F(2,47)= 17.01$, $p<0.0001$). Those with current AN differed from both the HC population ($F(1,47)=32.12$, $p<0.0001$) as well as the WR participants ($F(1,47)=15.07$, $p=0.0002$). Our weight restored participants and healthy control participants did not differ on current BMI ($F(1,47)=2.09$, $p=0.155$); however, collapsing across both clinical groups, participants with current or previous anorexia significantly differed from healthy controls ($F(1,48)=16.88$, $p=0.002$). For lowest BMI, there was an overall effect of group membership ($F(2,46)=47.28$, $p < 0.0001$) and a significant difference between both clinical groups and the healthy controls (AN vs. HC: $F(1,46)=70.60$, $p<0.0001$, WR vs. HC: $F(1,46)=67.65$, $p<0.0001$, (AN + WR) vs. HC: $F(1,46)=94.54$, $p<0.001$). In contrast, the difference between weight-restored participants and those with current anorexia was not significant ($F(1,46)=0.10$, $p=0.758$), indicating a similar level of previous symptom severity in our weight-restored participants as compared to the current symptom severity in our currently-ill participants.

For the tests of current eating disorder symptoms, all groups significantly differed on each of the EDE-Q subscales (Restraint: $F(2,49)= 37.28$, $R^2=0.603$, $p<0.001$; AN vs. HC: $F(1,49)=73.41$, $p<0.0001$, AN vs. WR: $F(1,49)=27.75$, $p<0.0001$, WR vs. HC: $F(1,49)=10.40$, $p<0.0022$, (AN + WR) vs. HC: $F(1,49)=46.80$, $p<0.0001$. Eating Concern: $F(2,49)= 43.98$, $R^2=0.642$, $p<0.0001$; AN vs. HC: $F(1,49)=86.33$, $p<0.0001$, AN vs. WR: $F(1,49)=33.77$, $p<0.0001$, WR vs. HC: $F(1,49)=11.55$, $p=0.001$, (AN + WR) vs. HC: $F(1,49)=54.19$, $p<0.0001$. Shape Concern: $F(2,49)= 55.98$, $R^2=0.696$, $p<0.0001$; AN vs. HC: $F(1,49)=109.62$, $p<0.0001$, AN vs. WR: $F(1,49)=43.93$, $p<0.0001$, WR vs. HC: $F(1,49)=14.05$, $p=0.0005$, (AN + WR) vs. HC: $F(1,49)=68.03$, $p<0.0001$. Weight Concern: $F(2,49)=57.24$, $R^2=0.700$, $p<0.0001$; AN vs. HC: $F(1,49)=114.29$, $p<0.0001$, AN vs. WR: $F(1,49)=33.52$, $p<0.0001$, WR vs. HC: $F(1,49)=23.22$, $p<0.0001$, (AN + WR) vs. HC: $F(1,49)=80.96$, $p<0.0001$. Global: $F(2,49)= 72.24$, $R^2=0.747$, $p<0.001$; AN vs. HC: $F(1,49)=142.73$, $p<0.0001$, AN vs. WR: $F(1,49)=51.86$, $p<0.0001$, WR vs. HC: $F(1,49)=21.56$, $p<0.0001$, (AN + WR) vs. HC: $F(1,49)=92.63$, $p<0.0001$). See Table 10.

Table 10: Eating disorder pathology (SD) by group. Significance tests (p<0.05): *a*=AN vs. HC; *b*=AN vs. WR, *c*=WR vs. HC, *d*= (AN+WR) vs. HC.

	AN Mean (SD)	WR Mean (SD)	HC Mean (SD)	Total Mean (SD)
Weight History				
• Current BMI	17.63 (1.28)	21.67 (2.12)	23.12 (2.12)	20.82 (3.68) [a,b,d]
• Lowest BMI	14.85 (1.72)	15.08 (1.76)	20.66 (2.30)	17.09 (3.35) [a,c,d]
EDE-Q Scores				
• Restraint	4.21 (1.22)	2.19 (1.17)	0.97 (0.96)	2.43 (1.74) [a-d]
• Eating Concern	4.94 (2.61)	3.59 (2.65)	2.39 (2.59)	3.62 (2.77) [a,d]
• Shape Concern	4.89 (0.84)	2.63 (1.17)	1.38 (0.92)	2.93 (1.75) [a-d]
• Weight Concern	4.58 (0.92)	2.60 (1.27)	0.98 (0.73)	2.68 (1.78) [a-d]
• Global	4.33 (0.76)	2.23 (1.08)	0.90 (0.66)	2.46 (1.65) [a-d]

In addition to examining eating disorder symptoms, we also investigated changes in temperament and character. For the harm avoidance subscale of the TCI, there was a significant overall effect of group membership ($F(2,49)=8.92$, $R^2=0.267$, $p=0.0005$). Both clinical groups differed from healthy controls (AN vs. HC: $F(1,49)=16.96$, $p=0.0001$ WR vs. HC, $F(1,49)=7.97$, $p=0.007$, (AN + WR) vs. HC: $F(1,49)=16.21$ $p=0.0002$), but did not differ from each other ($F(1,49)=1.63$, $p=0.208$), indicating that increased sensitivity to harm does not depend on malnutrition. There was no significant effect of group membership for novelty seeking ($F(2,48) = 1.47$, $p=0.240$), self-transcendence ($F(2,48)= 0.19$, $p=0.831$), persistence ($F(2,48)=1.24$, $p=0.298$), or cooperativeness ($F(2,46)=0.28$, $p=0.760$); however, there was an overall effect of group membership for reward dependence ($F(2,47)=3.54$, $p=0.037$), with follow-up tests indicating a difference between weight-restored and currently-ill participants ($F(1,47)= 7.08$, $p=0.011$). For self-

directedness, the overall model was significant ($F(2,48)=8.70$, $R^2=0.266$, $p=0.0006$) as were the contrasts between the currently-ill participants and controls ($F(1,48)=16.45$, $p=0.0002$), between participants with current anorexia and weight-restored participants ($F(1,48)=8.23$, $p=0.006$), and between clinical participants (AN + WR) and controls ($F(1,48)=9.17$, $p=0.004$). The difference between weight-restored participants and controls was not significant ($F(1,48)=1.41$, $p=0.241$). See Table 11.

To explore potential differences in social dysfunction, we tested for effects of group membership on overall AQ scores as well as in each of the three AQ subscales (i.e., social skills, details/patterns, and communication/mindreading). The full model for overall AQ scores was significant ($F(2,49)=5.97$, $R^2 = 0.196$, $p=0.005$). In the contrasts, participants with current anorexia did not differ from weight-restored participants ($F(1,49)=1.67$, $p=0.202$), but all other group comparisons were significant (AN vs. HC: $F(1,49)=11.68$, $p=0.001$, WR vs. HC: $F(1,49)=4.44$, $p=0.040$, (AN + WR) vs. HC: $F(1,49)=10.28$, $p=0.002$). For the AQ social skills subscale, there was a significant effect of group membership ($F(2,49)= 4.16$, $R^2=0.145$, $p<0.021$) with participants with current anorexia differing from healthy controls ($F(1,49)=8.32$, $p=0.006$) and aggregated clinical participants differing from healthy controls ($F(1,49)= 6.05$, p=0.175). No group differences emerged for either the details and patterns subscale or the communication and mind reading subscale of the AQ, suggesting that autism-like symptoms associated with AN are specifically related to social deficits. See Table 11.

Table 11: Temperament and Character Inventory (TCI) scores and Autism Spectrum Quotient (AQ) scores by group. Significance tests (p<0.05): *a*=AN vs. HC; *b*=AN vs. WR, *c*=WR vs. HC, *d*= (AN+WR) vs. HC.

	AN Mean (SD)	WR Mean (SD)	HC Mean (SD)	Total Mean (SD)
TCI				
• Harm Avoidance	21.94 (6.63)	19.24 (5.80)	13.33 (6.09)	18.08 (7.08) [a,c,d]
• Novelty Seeking	17.82 (7.98)	17.29 (5.96)	20.88 (5.56)	18.67 (6.64)
• Reward Dependence	14.76 (3.99)	18.24 (3.25)	16.38 (4.13)	16.46 (4.00) [b]
• Cooperativeness	36.00 (3.65)	36.88 (3.28)	36.75 (4.00)	36.55 (3.59)
• Self-Directedness	22.71 (9.31)	31.24 (7.60)	34.76 (9.00)	29.57 (9.91) [a,b,d]
• Self-Transcendence	15.35 (6.25)	14.53 (6.99)	14.00 (5.00)	14.63 (6.41)
• Persistence	6.44 (1.71)	6.18 (1.81)	5.44 (2.17)	6.00 (1.93)
AQ				
• Total Score	23.00 (5.83)	20.53 (6.06)	16.56 (4.79)	19.96 (6.09) [a,c,d]
• Social Skills	4.94 (2.61)	3.59 (2.65)	2.39 (2.59)	3.62 (2.77) [a,d]
• Details/ Patterns	5.06 (2.33)	5.12 (1.83)	4.33 (2.30)	4.83 (2.16)
• Communication/ Mind Reading	1.76 (1.30)	2.00 (1.37)	1.28 (1.13)	1.67 (1.28)

5.3.2 Effect of Clinical Status and Temperament on Social Functioning

To explore whether significant differences in affective biases, as indexed by the TCI, contributed to predictions of social deficits, we performed hierarchical regression analyses including clinical status ((AN + WR) vs. HC) at Step 1 and TCI subscale scores for harm avoidance and novelty seeking at Step 2. Because one participant failed to complete all items in the novelty seeking subscale, the total number of participants for

our hierarchical models vary (*Hierarchical Model 1 (Harm Avoidance)*: n=52; *Hierarchical Model 2 (Novelty Seeking)*: n=51; *Hierarchical Model 3 (Harm Avoidance & Novelty Seeking)*: n=51). At Step 1 for *Hierarchical Model 1*, the effect of clinical status was significant (Full Model: $F(1,50)= 5.90$, $R^2=0.106$, $p=0.019$; Clinical Status: $t(50)=2.43$, $p=0.018$). At Step 2, the inclusion of harm avoidance scores significantly improved model predictions for AQ social skills (Full Model: $F(2,49)= 5.61$, $R^2=0.1862$, $p<0.0064$; Clinical Status: $t(49)=1.11$ $p=0.273$, Harm Avoidance: $t(49)=2.20$, $p=0.033$; $\Delta F=4.86$, $\Delta R^2=0.082$, $p=0.032$). A similar but negative effect was found for the inclusion of novelty seeking at Step 2 for *Hierarchical Model 2* (Step 1, Full Model: $F(1,49)=5.44$, $R^2=0.10$, $p=0.024$; Clinical Status: $t(49)=2.33$, $p=0.024$. Step 2, Full Model, $F(2,49)= 9.11$, $R^2=0.275$, $p=0.0004$; Clinical Status: $t(48)=1.69$, $p=0.098$, Novelty Seeking: $t(48)=-3.41$, $p=0.0013$; $\Delta F=11.62$, $\Delta R^2=0.175$, $p=0.0013$). Including both harm avoidance as well as novelty seeking also performed significantly better than clinical status alone (*Hierarchical Model 3*: Step 1, Full Model: $F(1,49)=5.44$, $R^2=0.10$, $p=0.024$; Clinical Status: $t(49)=2.33$, $p=0.024$. Step 2, Full Model: $F(3,47)= 7.63$, $R^2=0.328$, $p=0.0003$; Clinical Status: $t(47)=0.62$ $p=0.540$, Harm Avoidance: $t(47)=1.91$, $p=0.062$, Novelty Seeking: $t(47)=-3.17$, $p=0.0027$; $\Delta F=7.96$, $\Delta R^2=0.228$, $p=0.0011$). The inclusion of novelty seeking in addition to harm avoidance and clinical status resulted in significantly better predictions of AQ social skills ($\Delta F=10.03$, $p=0.003$), and the inclusion of harm avoidance showed a trend towards better performance than a model including only novelty seeking and clinical status ($\Delta F=3.66$, $p=0.062$). See Table 12.

Table 12: Hierarchical models for clinical status, harm avoidance, and novelty seeking on social skills. [* Indicates $p<0.05$].

	Unstandardized Estimate (SE)	**Standardized Estimate (SE)**	***t*-value**
Hierarchical Model 1			
Step 1			
• Intercept	2.41 (0.65)	0	3.83*
• Clinical Status	1.88 (0.77)	0.33	2.43*
Step 2			
• Intercept	3.00 (0.66)	0	4.53*
• Clinical Status	0.95 (0.85)	0.16	1.11
• Harm Avoidance	0.12 (0.06)	0.33	2.20*
ΔR^2=0.08 ΔF=4.86 p=0.03			
Hierarchical Model 2			
Step 1			
• Intercept	2.41 (0.65)	0	3.72*
• Clinical Status	1.85 (0.79)	0.32	2.33*
Step 2			
• Intercept	2.81 (0.60)	0	4.69*
• Clinical Status	1.25 (0.74)	0.21	1.69
• Novelty Seeking	-0.18 (0.05)	-0.43	-3.41*
ΔR^2 =0.18 ΔF=11.62 p=0.001			
Hierarchical Model 3			
Step 1			
• Intercept	2.41 (0.65)	0	3.72*
• Clinical Status	1.85 (0.79)	0.32	2.33*
Step 2			
• Intercept	3.31 (0.64)	0	5.18*
• Clinical Status	0.51 (0.82)	0.09	0.62
• Harm Avoidance	0.10 (0.05)	0.27	1.91
• Novelty Seeking	-0.17 (0.05)	-0.39	-3.17*
ΔR^2=0.23 ΔF=7.96 p=0.01			

5.3.3 Mediating Role of Temperament on Disordered Eating and Social Functioning

In addition to exploring the relationship between clinical group and personality, we also wanted to examine how individual differences in current eating disorder symptoms related to social and affective factors. To do this, we tested whether novelty seeking or harm avoidance mediated the relationship between global EDE-Q scores and AQ social skills scores. Results indicated that in *Mediation Model 1 (Harm Avoidance)* there was a direct effect of global EDE-Q on AQ social skills (path c: β=0.620, t(50)=2.81, p=0.007). There was also an effect of global EDE-Q on harm avoidance (path a: β=2.522, t(50)=5.15, p<0.001). When both harm avoidance and global EDE-Q scores were included, there was a trend for harm avoidance to predict AQ social skills (path b: β=0.114, t(50)=1.83, p=0.074), but the effect of Global EDE-Q on AQ social skills scores was no longer significant (path c′: β=0.332, t(50)=1.25, p=0.219). The bootstrap analysis revealed a significant indirect effect of harm avoidance on AQ social skills (indirect effect ($\Delta\beta$) = 0.287, 95% confidence interval=[0.054, 0.582]), with harm avoidance mediating 46.4% of the total effect. Thus, harm avoidance fully mediated the relationship between global EDE-Q and AQ social skills. See Figure 10.

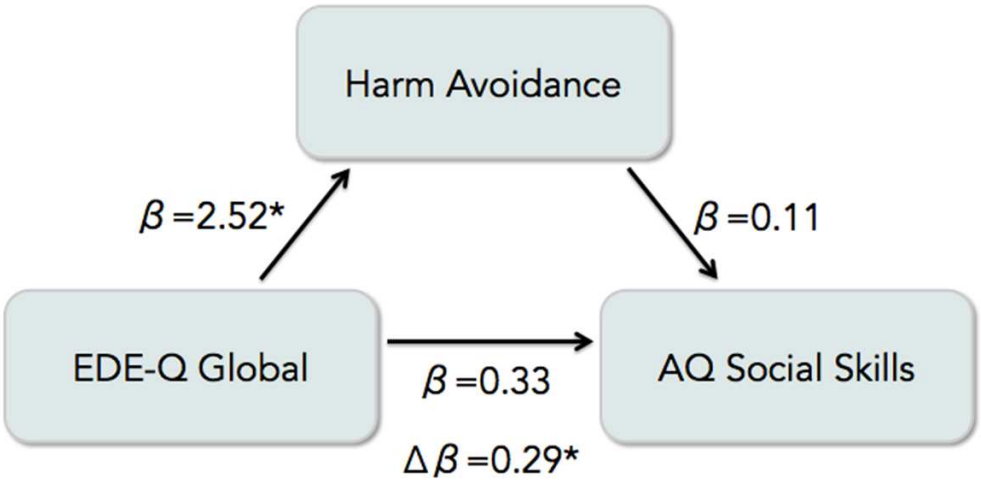

Figure 10: Mediation Model 1. Global scores on the Eating Disorder Examination Questionnaire (EDE-Q) predict scores on the social skills subscale of the Autism Spectrum Quotient (AQ); however, the inclusion of harm avoidance scores fully mediates the relationship between EDE-Q and AQ.

In *Mediation Model* 2 *(Novelty Seeking),* there was a direct effect of global EDE-Q on AQ social skills (path c: β=0.612, $t(49)=2.74$, $p=0.009$). The effect of novelty seeking on AQ social skills, however, was not significant (path a: β=-0.591, $t(49)=-1.05$, $p=0.300$). In the model including both global EDE-Q and novelty seeking, both variables were significantly associated with AQ social skills (path b: β=-0.184, t(49)=-3.64, $p=0.0006$; path c': β=-0.504, $t(49)=2.50$, $p=0.016$), but the indirect effect was not significant (indirect effect (Δβ) = 0.109, 95% confidence interval = [-0.128, 0.405]).

5.4 Discussion

A domain-general theory of affect posits that disturbances in core affective processing should manifest as disruptions across multiple psychological domains. Prior literature indicates that women with AN experience disturbances in the overall processing of affective information whereby core affective signals are both heightened and experienced as subjectively aversive. This bias in core affective processing, given a domain-general model of affect, should also be associated with increased aversion to social stimuli. To test this hypothesis, in the current study we examined the associations among eating disorder symptoms, affective biases in temperament, and social functioning.

Replicating previous findings, both currently-ill and weight-restored participants showed elevated levels of harm avoidance (Fassino et al., 2002; Klump et al., 2004; Klump et al., 2000), suggesting that individuals with AN show an increase in threat and harm sensitivity that is not dependent on being currently underweight. In contrast, we did not find evidence to support the conclusion that women with AN are lower overall in novelty seeking. A meta-analysis of previous studies using the TCI indicated that lower novelty seeking is a common but inconsistent finding in participants with AN (Harrison, O'Brien, et al., 2010). Thus, the small sample size in our study may have prevented the detection of subtle changes in reward sensitivity in clinical participants. Our results did, however, indicate a positive association between novelty seeking and

social functioning. Therefore, to the extent that patients show the trait of reduced novelty seeking, interventions that improve reward motivation may also show concomitant improvements in social functioning.

Prior studies have shown that women and adolescents with AN demonstrate higher levels of autism symptoms (Baron-Cohen et al., 2013; Hambrook et al., 2008). Here, we replicated that finding, showing that women with a current or previous diagnosis of AN have elevated total scores on the AQ as compared to healthy controls. Yet we did not find evidence for a categorical increase in all autism like traits (i.e., in each of the three AQ factors), but instead showed selective deficits in social functioning. Given a domain-general model of affect, social deficits in AN may arise from more fundamental disturbances in the processing of affect. Based on prior literature pointing both to heightened threat sensitivity (Harrison, Tchanturia, et al., 2010) and sensory sensitivity (Zucker et al., 2013) as well as disrupted reward processing in AN (Harrison, O'Brien, et al., 2010; Kaye et al., 2013), we explored whether changes in affective experiences could explain variance in AQ social skills scores above and beyond clinical status alone. Hierarchical models including either harm avoidance, novelty seeking, or both were significantly better at predicting social skills deficits than models including only clinical status. Taking a dimensional approach, the current degree of eating disorder symptoms across all participants was associated with social deficits; however, this association was fully mediated by the inclusion of scores on the harm avoidance

subscale of the TCI. Thus, supporting a domain-general account of affective processing, individuals that demonstrate more severe disruptions in eating behavior may demonstrate a constellation of related affective disruptions including increased threat sensitivity and social anxiety. This conclusion is consistent with other studies indicating that biases in affective processing can account for aspects of social deficits in AN (e.g., Adenzato, Todisco, & Ardito, 2012; Hambrook, Brown, & Tchanturia, 2012; Harrison, Sullivan, Tchanturia, & Treasure, 2009).

Neuroscientific data point toward a potential mechanism whereby biases in threat processing result in social dysfunction in AN. The insular cortex is known to encode core affective processes such as interoception (Craig, 2009; Craig, 2002) and physical pain (Brooks, Zambreanu, Godinez, Craig, & Tracey, 2005; Mazzola, Isnard, Peyron, Guénot, & Mauguière, 2009; Wiech et al., 2010). Yet studies in the field of social neuroscience have demonstrated that neural structures responsible for processing physical pain are also responsible for processing social pain (Dewall et al., 2010; Eisenberger et al., 2003; Eisenberger, 2012). Thus, alterations in the processing of bodily signals could also contribute to the pattern of increased sensitivity to social threat (Harrison, Tchanturia, et al., 2010) and heightened fear of negative social evaluation (Deboer et al., 2013; Gilbert & Meyer, 2005a, 2005b) associated with disordered eating.

In sum, our results suggest that social and interpersonal dysfunction in AN can be accounted for by changes in core affect. Potentially due to heightened sensory and

interoceptive reactivity, patients with AN become hyper-vigilant to threatening information in the environment. This results not only in a tendency to avoid primary reinforcers such as food, but also to withdraw from social situations. As a result, patients with AN fail to develop socioemotional expertise and show an increase in social cognitive dysfunctions mirroring those displayed in autism spectrum disorders.

6. Discussion

Constructionist models of emotion hypothesize that emotion is built out of basic psychological ingredients that in specific combination, produce discrete emotions. One prominent constructionist theory (Lindquist & Barrett, 2012) posits that emotion is comprised of two major properties, *core affect* and *conceptualization*. Core affect is defined as reactions arising from fluctuations in the state of the body that are subjectively experienced as valence (i.e., hedonic value) and arousal. Conceptualization, which is supported by other cognitive processes such as language and executive attention, helps situate the experience of core affect in context by drawing on knowledge of the world, prior learning, and current goals. It is through conceptualization that an individual is able to categorize and create meaning from core affective reactions as they pertain to the current circumstances.

Notably, while core affect and conceptualization are not specific to any particular emotion category, neither are they specific to emotion in general (Barrett, 2009). Both core affect and conceptualization are fundamental processes that contribute not only to emotion, but also to the construction of subjective reactions to reward and social stimuli. That is, *the basic properties contributing to the construction of affective processes are domain general.* The studies in this dissertation address the overlap in fundamental psychological and neural processes underlying emotion, reward, and social functioning. I have used both a basic science approach as well as clinical investigations to

demonstrate that emotion, reward processing, and social functioning are built on a common foundation and as such, are inextricably linked.

In Chapter 2, I presented a study investigating the overlap between emotion and reward processing, and demonstrated that the vmPFC is responsible for encoding value not simply across different reward modalities, but also for emotional stimuli. In addition to showing that aspects of core affect are shared across reward and emotional processing, I have also shown that disruptions to the fundamental building blocks of affect produce deficits that are not domain specific. Individuals with AN are characterized by decreased motivation to pursue reward and increased motivation to avoid harm (Harrison, O'Brien, et al., 2010). This profile is broadly suggestive of a skew in the experience of core affect, whereby individuals with the disorder are more likely to experience stimuli as aversive and less likely to experience them as appetitive. This bias in the processing of hedonic value may be due in part to disturbances in either the ability or willingness to process fluctuations in sensations arising from the body. These disturbances, combined with the inflexible use of emotion regulation and rigid behavioral control (i.e., disturbances in conceptualization), contribute to the development of disordered eating behaviors, but also to a range of social and emotional disturbances.

In Chapter 4, I showed that women with a history of AN show ongoing pathological eating as well as increased social anxiety. Moreover, I demonstrated that

the degree of eating-related psychopathology is related to differential social processing in the neural mechanisms of core affect. In Chapter 5, I expanded on these results by examining the relationship between aversive temperament and social dysfunction. In the following sections, I will summarize the findings from each of these studies and discuss their relevance to a domain-general theory of affective processing.

6.1 Summary of Findings and Their Relevance to a Domain-General Constructionist Model of Affect

Previous research points to two conflicting accounts of the role of the vmPFC in affective processing. The field of neuroeconomics has strongly implicated the vmPFC in encoding reward value (Levy & Glimcher, 2012). In contrast, studies of negative emotion regulation suggest that this region is important for controlling affective responses (Diekhof, Geier, Falkai, & Gruber, 2011). Because most studies of emotion regulation focus only on negative emotional responses, it is impossible to determine from these studies whether the vmPFC activation elicited by emotion regulation is the result of cognitive control or a shift in the value of emotional stimuli when they move from a more negative to a more neutral (and thereby more positive) state.

In Chapter 2, I presented a study in which I investigated the neural mechanisms of emotional valuation and regulation. Two independent experimental samples of participants performed a cognitive reappraisal task while undergoing functional magnetic resonance imaging (fMRI). The experience of positive emotions activated the vmPFC, while the regulation of positive emotions led to relative decreases in vmPFC

activation. During the experience of positive emotions, vmPFC activation tracked participants' own subjective ratings of the valence of stimuli. Furthermore, vmPFC activation also tracked normative valence ratings of the stimuli when participants were asked to experience their emotions, but not when asked to regulate them. A separate analysis of the predictive power of vmPFC on behavior indicated that even after accounting for normative stimulus ratings and condition, increased signal in the vmPFC was associated with more positive valence ratings. Collectively, these results suggest that the vmPFC encodes a domain-general value signal that tracks the value of not only of external rewards, but also emotional stimuli. In this way, the vmPFC encodes a domain-general signal for hedonic value.

One of the critical points of the constructionist model of emotion is that emotional responses are situated in context. That is, the subjective emotional response that is ultimately experienced depends on prior learning and current goals. In the study presented in Chapter 2, on half of all trials, participants were asked to attempt to alter their emotional responses via regulation. This goal of altering affective responses is also reflected in vmPFC activation. When participants were asked to reappraise, they were highly successful, assigning a neutral rating (i.e., a 4 or a 5) on the overwhelming majority of trials. This flattening of the subjective behavioral reports corresponded to a vmPFC response that was also essentially flat. Thus, the vmPFC encodes core affect in that it represents hedonic value; however, the representation of hedonic value in the

vmPFC does not correspond to the objective value of stimuli but rather to a subjectively encoded hedonic value that also incorporate aspects of conceptualization.

In addition to basic science approaches, the study of psychiatric disorders offers a unique opportunity to investigate how a system works by elucidating the ways in which it breaks down. At face value, AN seems to be a disorder of reward function. Individuals with AN are frequently described as ascetic (Fassino et al., 2006), and they eschew food in favor of longer-term weight loss goals (Kaye et al., 2009). Yet, consistent with a domain-general account of affective processing, individuals with AN also experience profound disturbances in social and interpersonal functioning. In Chapter 4, I presented a study probing the neural mechanisms of affective disturbance in AN and how the engagement of these mechanisms is different during social processing. In this study, weight-restored women with a history of AN and healthy control women underwent fMRI while they viewed images of female faces, female bodies, and scrambled images. They also completed survey measures to index current eating disorder symptoms and social functioning.

Results indicated that women with a history of AN showed increased anxiety about social evaluation and elevated levels of disordered eating. Irrespective of group, social anxiety explained the current level of eating disorder symptoms, suggesting that social dysfunction may be a predisposing or maintaining factor for disordered eating. Clinical participants also showed differences in both cognitive and perceptual regions of

the brain when viewing images of bodies. Furthermore, all participants' current level of eating disorder symptom severity was associated with increased activation in the insula when viewing faces. These results point to ongoing neural and behavioral disturbances in social functioning in AN even after recovery.

The constructionist model of emotion implicates the insula in core affect (Lindquist & Barrett, 2012; Lindquist et al., 2012), but more specifically in attention directed to the body. The insula may track changes in bodily homeostasis, signaling the presence of salient stimuli in the current environment. This information is then used to control behavior based on the assessment of salient stimuli (Lindquist & Barrett, 2012). Changes in insular processing have frequently been observed in both currently-ill and recovered patients with AN (see Table 1). Moreover, women with AN display changes in somatosensory (Keizer et al., 2011, 2012) and interoceptive perception (Pollatos et al., 2008). Thus, one of the fundamental changes in AN is in the ability to use information arising from the body to guide behavior. There is debate as to whether this deficit arises due to a primary inability to sense interoceptive changes (e.g., Pollatos et al., 2008) or due to an avoidance of interoceptive sensations resulting from heightened visceral reactivity (Zucker et al., 2013). Regardless of the nature of the disturbance, a domain-general account of affective processing would posit that disruptions in the fundamental bases of core affect would disrupt processing across affective domains. Indeed, disruptions in insular function in AN have been observed in response to physical stimuli

(Strigo et al., 2013) and rewards (Wagner et al., 2008) as well as emotionally evocative stimuli (Miyake et al., 2010). In the study presented in Chapter 4, eating disorder symptom severity was associated with increased response in the insula to face images. The current level of eating disorder symptoms was also associated with increased anxiety over social evaluation. Thus, increased insular response to faces in individuals with high levels of disordered eating might reflect a visceral response to social stimuli that tags these stimuli as threatening more or less automatically. This could explain previous data demonstrating that patients have an attentional bias towards threatening faces (Harrison, Tchanturia, et al., 2010) and a tendency to report greater social anxiety (Hinrichsen et al., 2003).

Chapter 5 builds on this hypothesis by exploring the relationship between social dysfunction and affective temperament. High levels of harm avoidance and low levels of novelty seeking have been observed in patients with AN (Harrison, O'Brien, et al., 2010). These findings suggests that—when considering core affective responses as falling along a continuous scale of valence ranging from highly negative to highly positive—individuals with AN experience stimuli as skewed towards the negative end of the scale. Given that social situations are fundamentally affective in nature, a bias in the processing in core affect could explain interpersonal difficulties in AN. In the study presented in Chapter 5, healthy control women, women with a current diagnoses of AN and women with a previous diagnoses of AN but who were currently weight restored

completed survey measures of social functioning and temperament and character. Results indicated that both harm avoidance and novelty seeking contributed to predictions of social dysfunction (in different directions). Furthermore, variation in harm avoidance fully mediated the relationship between current eating disorder symptoms and social skills deficits as indexed by the autism spectrum quotient. These results suggest that increased harm sensitivity may contribute to the development and maintenance of social dysfunction in AN. In our sample, we did not find evidence that women with current or past AN were different from control women in novelty seeking; however, our analyses did indicate that novelty seeking was negatively associated with social dysfunction. Albeit less consistently that increased harm avoidance, lower novelty seeking has been observed in women with AN (Harrison, O'Brian, et al., 2010). Thus, a general behavioral profile of increased threat sensitivity and less appetitive drive may contribute towards the development of both disordered eating and poor interpersonal functioning.

The evidence presented in Chapters 4 and 5 supports the conclusion that patients with AN experience consistent and domain-general disruptions in affective processing, with affective stimuli frequently being experienced as emotionally aversive regardless of whether they are social, emotional, or reward-related. Such a bias could account for the avoidant behavior these patients demonstrate across a wide range of circumstances. For example, women with AN report an unwillingness to experience emotion (Merwin et al.,

2013) as well as sensory sensations (Zucker et al., 2013). Furthermore, they frequently avoid interpersonal conflict (Lattimore, Wagner, & Gowers, 2000) and are socially inhibited in general (Carter, Kelly & Norwood, 2012).

Broadly, these results suggest that disruptions in the subjective experience of core affect are responsible for avoidant behavior in AN. Yet how domain-general affective avoidance might emerge in AN is not well understood. A view that has gained growing support is that women with AN experience heightened visceral and interoceptive sensitivity (Kaye et al., 2009; Zucker et al., 2013), but an increase in the intensity of bodily signals does not necessarily mean these signals will be subjectively experienced as aversive. In normal individuals, highly arousing visceral sensations are often experienced as pleasant and even positively reinforcing. The sensation that one's stomach is dropping just as a rollercoaster car begins its descent is a feeling that no doubt drives many regular amusement park goers. In these cases, roller coaster enthusiasts interpret this intensely visceral sensation as hedonically positive, in part because of its association with positive outcomes. The roller coaster enthusiast knows—unless she is attending the North Carolina State Fair—that she will be safe. Furthermore, she experiences the ride as thrilling, an opportunity to display her own bravery, and a chance to bond with her social group.

In contrast to this example, patients with AN may have learned to associate bodily sensations—hunger, satiety, sexual arousal—with negative outcomes. Given the

broader cultural context in which dieting is encouraged and thinness is prized, individuals who are predisposed to develop disordered eating may associate feelings of fullness or digestion with guilt, anxiety, and shame. As these associations are strengthened over time, bodily sensations may begin to trigger negative affective responses rapidly, potentially even before food has been consumed. In an effort to reduce the negative affect associated with interoceptive processing, patients with AN may attempt to consciously control the bodily states they experience through dietary restraint. Such efforts may be positively reinforced in at least two ways. First, by controlling consumption, patients who develop disordered eating reduce the negative feelings that arise when they consume food. Over time, once a starvation state is achieved, visceral signals of any kind may be reduced, which results in an overall reduction in negative affect. Second, when patients first begin to lose weight, they may be subtly or overtly encouraged by friends and family, which reinforces the behavior. Once this tendency to control emotional reactivity through starvation has become habitual, however, the behavior may be less sensitive to changes in the nature of the feedback elicited by it. Thus, by the time patients are severely underweight, negative feedback from peers, family members, and healthcare provides may do little to alter behaviorally and neurally engrained disordered eating.

Self-regulation also may contribute to the domain-general affective biases observed in AN. Patients with AN have long-term goals to lose weight and control

dietary intake and may engage in maladaptive emotion regulatory strategies that help them achieve these goals. While some of these emotion regulatory attempts may be consciously deployed, others may be employed outside conscious awareness. For comparison, consider socioeomotional functioning in older adults. As people age, they perceive time as limited, and begin to prioritize social and emotional goals (Carstensen, Isaacowitz, & Charles, 1999). To achieve goals to optimize emotional well-being, older adults engage in a number of emotion regulatory strategies that allow them to preferentially process negative stimuli less, resulting in the widely-cited "positivity bias" observed in memory, attention, and decision making (Carstensen & Mikels, 2005; Fung & Carstensen, 2003; Mather & Carstensen, 2005; Reed & Carstensen, 2012). The bulk of evidence on the positivity bias suggests that emotion regulation strategies that result in the positivity bias are largely unconscious (e.g., Allard, Wadlinger, & Isaacowitz, 2010; Mather & Knight, 2005). A similar process may be at work in AN, whereby weight loss goals are chronically activated, and self-regulatory strategies that increase the likelihood of achieving these goals are automatically and chronically engaged. Given that the neural mechanisms for affective processing are shared, these chronically-activated strategies to regulate food intake may have unintended consequences for other affective functions. That is, strategies that may increase aversive reactions to food may also contribute to increased withdrawal responses to emotional and social stimuli.

6.2 Applications for the Domain-General Constructionist Model of Affect to Other Psychiatric Disorders

One of the major goals of this dissertation is to understand how a domain-general theory of affective processing can account for disruptions in AN; however, as I alluded to in Chapter 3, this theory has relevance for a broad range of psychiatric disorders. Many psychiatric disorders are characterized by disturbances in affective processing, and these disturbances tend to impact functioning across many psychological domains. Furthermore, there is often a high degree of comorbidity between disorders with conceptually similar disruptions in affective processing. Patients with major depressive disorder and anxiety disorders show a similar pattern of behavioral biases whereby both groups show increases in negative affectivity (Watson, Clark, & Carey, 1988), increased attention to negative stimuli (Leyman, De Raedt, Schacht, & Koster, 2007; Mogg, Millar, & Bradley, 2000), and maladaptive rumination (Yook, Kim, Suh, & Lee, 2010). Moreover, both groups show increased activation in regions of the brain involved in core affect (i.e., in the insula) (van Tol et al., 2012) and decreased activation in regions thought to be important for conceptualization (i.e., the prefrontal cortex) (Beutel, Stark, Pan, Silbersweig, & Dietrich, 2010; Taylor & Liberzon, 2007). Thus, consistent with a domain-general model of affect, across similar psychiatric conditions the neural and psychological biases in affective processing are often analogous.

Classifying affective disturbances in psychiatric conditions as general disruptions that span all affective domains might initially make the problem of treating psychological disorders seem intractable. However, upon deeper consideration, this conceptual approach could dramatically simplify the problem of treatment by pointing to areas of intervention that can improve functioning across domains. For example, women with AN often feel ambivalent about engaging in treatment (Colton & Pistrang, 2004; Strober, 2004). As the nature of the disorder is such that patients experience intense fear of gaining weight, they may have little motivation to begin treatments that focus on altering eating behavior. In contrast, many patients with AN report a desire to improve interpersonal functioning and may be more willing to engage in treatments that specifically target social functioning (see Zucker et al., 2007 for a discussion). If the psychological and neural mechanisms responsible for affective processing in response to social as well as primary rewards are shared, psychological interventions that aim to improve how core affect is experienced and how these experiences are conceptualized in social situations may nonetheless improve affective functioning in response to food and the body as well. A similar approach may also be effective for other psychiatric disorders. For example, if patients with obsessive-compulsive disorder learn to routinely use emotion regulation strategies to alter their affective responses to stimuli other than those that trigger their specific obsessive thoughts or compulsive behaviors, as they

become skilled at employing such strategies, they may additionally begin improve their abilities to control their pathological thoughts and behaviors.

6.3 Final Conclusions

The framework proposed in this dissertation has broad relevance for understanding the fundamental building blocks of human affective experience. Regardless of the exact nature of an affectively charged stimulus, bodily responses that guide the intensity and valence of the response (i.e., core affect) as well as cognitive processes that interpret and manipulate the meaning of the stimulus in context (i.e., conceptualization) will contribute to the subjective feeling evoked by that stimulus, and ultimately, the behavioral response. Understanding how domain-general affective signals are encoded in the brain and how they manifest across psychological functions can lead to a better understanding of affective functioning in both healthy individuals as well as those with psychiatric impairments.

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Biography

Amy A. Winecoff was born January 24th, 1984, in Albemarle, North Carolina. She graduated valedictorian, Phi Beta Kappa, and summa cum laud with a Bachelor of Arts in Arts Applications in 2007 from North Carolina State University. After graduation she worked as a Post Baccalaureate Fellow in functional neuroimaging at Duke University's Brain Imaging and Analysis Center. In the fall of 2009, she joined the Duke University graduate school through the Cognitive Neuroscience Admitting Program and was awarded the James B. Duke Graduate Fellowship. After rotating in the laboratories of Nancy Zucker, Roberto Cabeza, and Michael Platt, she ultimately joined the laboratory of Scott Huettel. She has published papers in *Social Cognitive and Affective Neuroscience*, *Journal of Neuroscience, Frontiers in Neuroscience,* and *Brain Research.* In the fall of 2014, she will begin work as an assistant professor of psychology at Bard College.