CHAPTER 3

How We Heal What We Don't Want to Feel

THE FUNCTIONAL NEURAL ARCHITECTURE OF EMOTION REGULATION

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Whether trying to mollify a fear of flying or keep one's cool in rush-hour traffic, the need to adaptively regulate emotion is ubiquitous. Perhaps because of its ubiquity, in the past decade behavioral and biological research on emotion regulation has exploded. Much of this work has sought to clarify the consequences of specific regulatory strategies and the contexts in which they are most appropriately used (Gross, 1998b). Other work has attempted to delineate the functional neural architecture underlying emotion and emotion regulation (Ochsner & Gross, 2005, 2007, 2008). This work offers an opportunity to determine what neural mechanisms allow a healthy individual to keep an even keel, to examine how the operation of these mechanisms varies across healthy individuals, and, perhaps of greatest interest for the present volume, to examine how the coordination of these neural mechanisms might falter in psychopathology.

This chapter seeks to address these questions about the neural bases of emotion and emotion regulation in four parts. In the first part, we provide a framework for understanding how emotion regulation may alter the process of generating an emotion, and focus on a particular cognitive emotion regulation strategy known as reappraisal. In the second part, we briefly review neuroimaging methods used in the field, followed by a review of evidence for a working model of the neural bases of emotion regulation. In the third part, we apply this model to understanding the typical range

of variation in individual differences in emotion and its regulation. Finally, in the fourth part, we apply this model to elucidate emotion dysfunction across clinical disorders, including schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders, including posttraumatic stress disorder.

Models of Emotion and Emotion Regulation

Although there are various conceptualizations of emotion, throughout this chapter we follow appraisal theorists by treating emotion as a continuously unfolding process of assessing the significance of a stimulus to one's current goals, wants, and needs (Barrett, Ochsner, & Gross, 2007; Scherer, Schorr, & Johnstone, 2001). This appraisal process produces a set of behavioral, experiential, and physiological response tendencies appropriate for the eliciting stimulus. Emotional responses are relatively transitory and tied to a specific elicitor, in contrast to moods, which are objectless and enduring (Barrett et al., 2007; Gross, 1998a, 1998b). On this view, affect denotes a superordinate category that encompasses emotion and moods and includes any valenced response to a stimulus.

Against this backdrop, emotion regulation can be seen as any explicit or implicit process that alters which emotions an individual feels, how long they feel them, and how they express them (Gross, 1998b; Ochsner & Gross, 2005). In general, there are two classes of emotion regulation strategies. Behavioral strategies involve acting to avoid exposure to an emotion-eliciting stimulus, changing the nature of the emotion-eliciting stimulus to which one is exposed, or controlling the behavioral expression of the emotion (e.g., suppression). By contrast, cognitive strategies modify the way in which one attends to and represents the meaning of the emotional event. Each of these strategies may be used to down-regulate or up-regulate emotion, depending on one's goal.

The remainder of this chapter focuses on cognitive strategies for controlling emotion in general and on one strategy in particular, known as reappraisal (i.e., reinterpreting the meaning of a stimulus in ways that alter its emotional impact) for two reasons. First, the bulk of human neuroscience research on emotion regulation has been devoted to studying reappraisal (Ochsner & Gross, 2008). Second, behavioral work has shown that reappraisal is highly effective for enhancing positive and reducing negative emotion and promoting interpersonal relationships (Gross, 1998a; Gross & John, 2003), thus pointing to its importance as a healthy strategy to promote in psychopathology research. What's more, it does so without the negative consequences associated with some strategies, such as suppression. Relative to reappraisal, suppression impairs memory and increases physiological responding (Gross, 1998a; Richards & Gross, 2000).

A Neural Model of the Cognitive Control of Emotion

By and large, our knowledge of the neural bases of emotion and its regulation comes from human functional neuroimaging studies. In this section, we draw on this literature to build a working model of how the brain implements the appraisal processes that give rise to emotions and the cognitive control processes that enable us to regulate them. Before doing so, however, it may be useful to quickly review the two neuroimaging modalities that serve as the basis of our literature review: functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

PET and fMRI: Strengths and Weaknesses

The great advantage of both PET and fMRI is that they allow brain function to be assessed in awake, behaving participants who may or may not have some sort of clinical disorder. Both methods have limitations that should be noted, however. fMRI provides excellent spatial resolution and relatively good temporal resolution for structural and functional brain imaging, but it does not directly measure neuronal activity. Rather, fMRI measures the blood oxygen level–dependent (BOLD) response, which corresponds to the ratio of oxygenated to deoxygenated hemoglobin across multiple areas of the brain, a ratio thought to indirectly reflect the local field potential of neurons in a given region (Wager, Hernandez, Jonides, & Lindquist, 2007). One major drawback of fMRI is that, because it is sensitive to magnetic properties of the blood, noise can be introduced into its measurement by any factors that generate or alter magnetic fields, including pockets of air, as found in our sinus cavities, and fluids, as found in the ventricles and large draining veins. This means that imaging some regions critical for emotion, like the amygdala, can be difficult because they lie close to the bottom of the brain at the anterior tips of the temporal lobes, adjacent to the anterior tips of the lateral ventricles, not far from large arteries and veins in the brainstem and just behind some sinuses cavities. By contrast, PET provides a direct measurement of glucose metabolism and is not subject to magnetic susceptibility artifacts as is fMRI. The major drawbacks of PET are that it involves ionizing radiation exposure (Grubb, Raichle, Higgins, & Eichling, 1978) and has comparatively lower spatial and temporal resolution relative to fMRI (Wager et al., 2007). Whereas typical fMRI can be sensitive to changes occurring as fast as every second, PET studies average activity across time windows of 60 seconds or more.

Experimental design in fMRI and PET commonly involves the subtraction method (Posner, Petersen, Fox, & Raichle, 1988), wherein activity corresponding to the performance of a control task or behavioral state is essentially subtracted from activity corresponding to a critical task state. The result is a difference map reflecting the neural processes selectively

activated during the performance of the task. Causality remains unclear, however, in such analyses because the resulting map of brain activation is only *correlated* with one task state or another. Still, many neuroimaging studies use this logic to draw inferences about differential neural systems involved in the performance of different behavioral tasks. As described later, the strength of correlations between individual differences in brain activation over a particular neural region of interest and individual differences in a behavioral measure can provide additional information about brain systems critically involved in task performance.

Neural Bases of Emotional Appraisal and Reappraisal

Although numerous studies have investigated the brain systems involved in emotional learning and response, our working model primarily derives from studies that have directly compared neural systems involved in emotion appraisal and regulation in the same paradigm. Such experiments simultaneously provide insights into the mechanisms of emotion generation and regulation. Because of space limitations, this sketch is brief, and interested readers are directed to more detailed discussions of it elsewhere (Ochsner & Gross, 2005, 2007).

Neural Bases of Emotional Appraisal

Our working model specifies roles in emotional appraisal for several brain structures that have consistently been shown to be activated during the perception of emotional stimuli and modulated during reappraisal of responses to them. We collectively refer to these brain regions as the neural bases of emotional appraisal: the amygdala, the insula, the striatum, and the medial orbitofrontal cortex. These regions are illustrated in Figure 3.1. Although this model does not include every neural region relevant to emotional appraisal, it does include the principal components based on the current literature. Critically, all components of this model were shown to be consistently activated in a comprehensive meta-analysis of 162 neuroimaging studies that examined the functional grouping of brain regions involved in emotion regardless of the specific type of emotion (e.g., fear or anger) included in each of the studies (Kober et al., 2008).

AMYGDALA

The amygdala is a pair of bilateral almond-shaped structures containing multiple nuclei located in the tip of the temporal lobe. Rodent and other small-mammal studies have noted that the lateral nucleus of the amygdala exhibits marked plasticity during the acquisition of fear conditioning; the firing rate of lateral amygdala neurons has been shown to dramatically

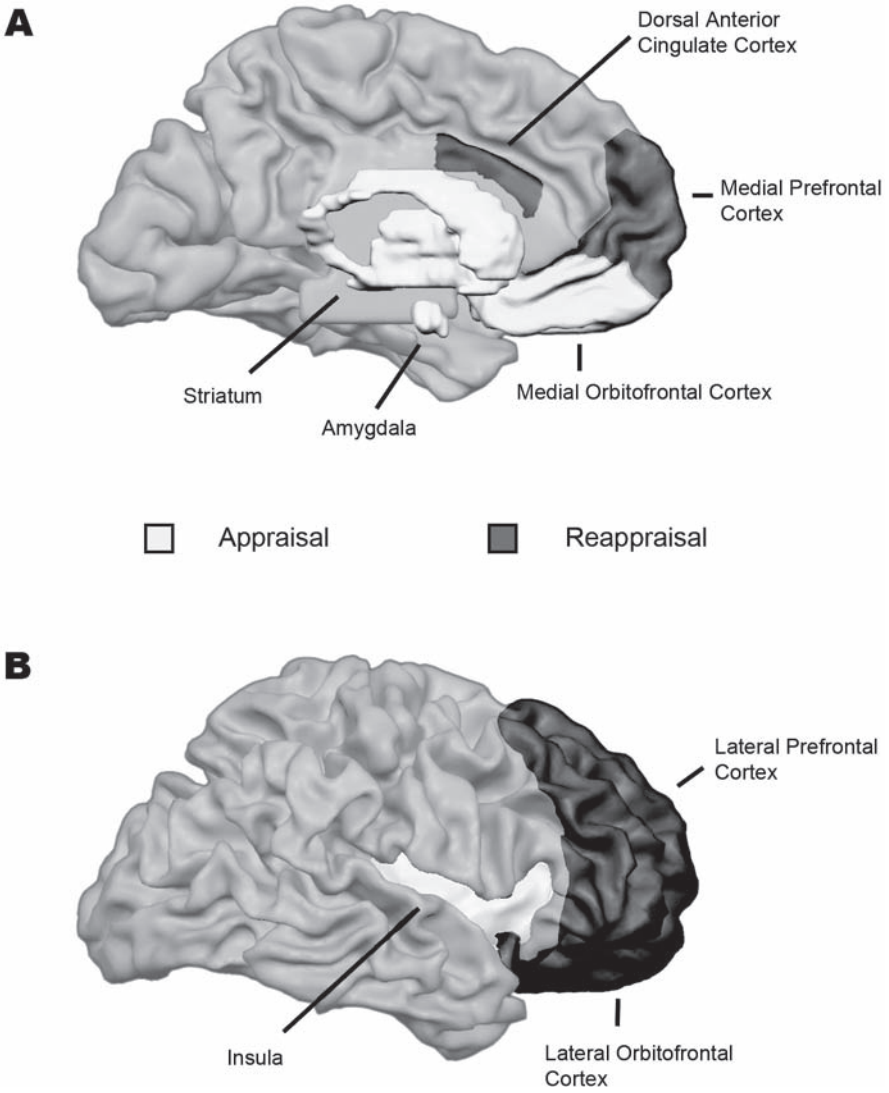

FIGURE 3.1. Overview of the working model for the functional architecture of appraisal and reappraisal. (A) Medial view of the brain showing the amygdala, striatum, and medial orbitofrontal cortex, all related to emotional appraisal. Also shown are the dorsal anterior cingulate cortex and the medial prefrontal cortex, which are important for reappraisal. (B) Lateral view of the brain showing the insula, involved in emotional appraisal, and the lateral prefrontal cortex and lateral orbitofrontal cortex, involved in reappraisal. (Color figure is available at *www.guilford.com*.)

increase during that time (Quirk, Repa, & LeDoux, 1995). However, the basolateral complex of the amygdala (consisting of the basal and lateral nuclei) has been shown to be critical for the expression of conditioned fear (Maren, Aharonov, & Fanselow, 1996). A substantial human neuroimaging literature points toward the amygdala's importance in emotional appraisal as well. In parallel with the rodent evidence, many studies have found associations between amygdala activity and the detection of rapidly (even subliminally) presented stimuli that connote the presence of potential threats, like facial expressions of fear and anger and images of threatening situations (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Whalen et al., 1998). Importantly, several studies have reported decreased amygdala activity during down-regulation of negative emotion via reappraisal (Goldin, McRae, Ramel, & Gross, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner, Ray, et al., 2004; Phan et al., 2005; van Reekum et al., 2007).

It should be noted that amygdala activation is not solely associated with fear, or even negative emotion. Indeed, several neuroimaging studies have implicated the amygdala in the appraisal of positively valenced stimuli such as sexual images, appealing animals, and appetizing food as well as high-interest, unusual images (e.g., surrealistic images) (Hamann, Ely, Hoffman, & Kilts, 2002). Furthermore, amygdala activation has been shown to not differ in processing positive and negative pictures (Garavan, Pendergrass, Ross, Stein, & Risinger, 2001). Thus, the amygdala is theorized to broadly detect whether a stimulus is emotionally salient in our working model.

INSULA

Based on its connectivity, the insula has been characterized as many things, including a visceral sensory area, a somatosensory area, a motor association area, a language area, and a "limbic" integration cortex, among others (Augustine, 1996). All of this suggests that functional neuroimaging evidence should support a role for the insula in emotional appraisal, which likely draws on all these modalities of information to assess the affective significance of a stimulus. Indeed, studies have implicated the anterior portion of the insula in particular in response to, and likely in the aversive experience of, various kinds of aversive stimuli, although lesion studies suggest it may play a special role in the perception and experience of disgust, perhaps because it receives ascending information from the viscera (Damasio et al., 2000; Lévesque et al., 2003; Phillips et al., 1997; Wager & Barrett, 2004; Wager et al., 2008; Wicker et al., 2003). Like the amygdala, the insula has shown diminished activity during the down-regulation of negative emotion via reappraisal in several studies (Goldin et al., 2008; Ochsner et al., 2002; Ochsner, Ray, et al., 2004; Phan et al., 2005).

STRIATUM

Two subcortical regions, the caudate and the putatmen, are referred to collectively as "the striatum." Both the dorsal and ventral striatum have been shown to be involved in human reward processing (O'Doherty et al., 2004). In particular, the dorsal striatum has been linked to processing reward outcomes (Delgado, Locke, Stenger, & Fiez, 2003; O'Doherty et al., 2004), while the ventral striatum, and particularly the nucleus accumbens, has been linked to processing the anticipation of reward (Knutson, Adams, Fong, & Hommer, 2001).

Furthermore, nearly 70% of neuroimaging studies involving happiness induction have reported activation in the basal ganglia, which includes the striatum, according to a meta-analysis (Phan, Wager, Taylor, & Liberzon, 2002). The striatum is not simply a "reward organ," however, and may play a more general role in mediating habitual responses (Fernandez-Ruiz, Wang, Aigner, & Mishkin, 2001). Thus, any stimulus that is relevant to learning or expressing meaningful sequences of thoughts or actions may activate the striatum, including nonrewarding but unexpected salient stimuli (Zink, Pagnoni, Martin, Dhamala, & Berns, 2003) and facial expressions of disgust (Phillips et al., 2004; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). Striatal activity in the nucleus accumbens has been shown to be diminished during down-regulation of negative emotion via reappraisal (Phan et al., 2005). However, other researchers have shown that the dorsal striatum is engaged during reappraisal (Ochsner, Ray, et al., 2004; van Reekum et al., 2007), which could reflect either learning to regulate more effectively or the generation of positive responses to a stimulus during down-regulation of negative emotion, or both. Thus, the striatum is clearly involved in emotional appraisal, although its precise involvement in reappraisal is not clear.

MEDIAL ORBITOFRONTAL CORTEX

Brain imaging studies have implicated the medial OFC (MOFC), which has interconnections with all of the appraisal-related structures mentioned previously, in maintaining representations of the affective value of a stimulus, such as a rewarding rather than punishing monetary outcome (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001) or an attractive face (O'Doherty et al., 2003), in the context of one's current goals. This means that MOFC will rapidly change its response to a stimulus that once was rewarding but now is not (Rolls, 2000). In the domain of reappraisal, attending to a negative stimulus rather than reappraising it has also been associated with activation in the MOFC (Ochsner et al., 2002). Notably, Ochsner, Ray, and colleagues (2004), in a replication and extension of Ochsner and colleagues' (2002) study, did not observe modula-

tion of MOFC activity by reappraisal, although the authors note that this may have been due to greater instruction to attend to one's feelings in the initial study relative to an instruction to simply respond naturally in the latter study. As such, context is thought to play a large role in determining whether MOFC activation is observed during emotional appraisal.

Neural Bases of Reappraisal

Several brain structures have been implicated consistently in reappraisal studies: the lateral prefrontal cortex (LPFC), the medial PFC (MPFC), the dorsal anterior cingulate cortex (dACC), and the lateral OFC (LOFC) (see Figure 3.1). The common thread connecting these brain regions during reappraisal is likely the need to create and maintain a regulatory strategy, to integrate newly constructed top-down interpretations of stimuli and continuing bottom-up appraisals of those stimuli, and to reinterpret the meaning of internal states relevant to the stimuli being reappraised (Ochsner & Gross, 2004).

LATERAL PREFRONTAL CORTEX

Evidence from neuropsychological patients and from functional neuroimaging suggests that the dorsolateral PFC (DLPFC) is important for maintaining and manipulating information in working memory, including during reasoning and problem solving (Barcelo & Knight, 2002; Callicott et al., 1999). Especially relevant to reappraisal, which involves selecting appropriate reinterpretations of stimuli, are portions of the ventrolateral PFC (VLPFC) that have been associated specifically with selecting among competing representations of task-appropriate knowledge (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005).

The lateral PFC has been consistently activated in reappraisal paradigms, potentially reflecting increased knowledge selection. Studies have implicated both the DLPFC and VLPFC during down-regulation of negative emotion via reappraisal (Goldin et al., 2008; Ochsner et al., 2002; Ochsner, Ray, et al., 2004; Phan et al., 2005). Furthermore, Ochsner, Ray, and colleagues (2004) have also reported DLPFC and VLPFC activity during up-regulation of negative emotion, strengthening its proposed role as a component of the reappraisal system.

MEDIAL PREFRONTAL CORTEX

The MPFC has been strongly implicated in making judgments about internal mental states rather than externally generated information (Lieberman, 2007; Ochsner, Knierim, et al., 2004). In addition, the MPFC has been shown to be particularly active when making self-referential judgments (Kelley et al., 2002; Ochsner, Knierim, et al., 2004) and self-focused

(rather than situation-focused) reappraisals when down-regulating negative emotion (Ochsner, Ray, et al., 2004). It has been suggested that MPFC varies along its dorsal to ventral and caudal to rostral extents in terms of the explicitness with which it represents affective and mental state information. On this view, increasingly rostral and dorsal portions process increasingly explicit representations about mental states (Amodio & Frith, 2006; Gallagher & Frith, 2003; Olsson & Ochsner, 2008).

MPFC, including dorsal MPFC, has also been associated with both the down- and up-regulation of emotion as well as selective attention to emotional states (Goldin et al., 2008; Ochsner et al., 2002; Ochsner, Hughes, Robertson, Cooper, & Gabrieli, in press; Ochsner, Ray, et al., 2004; Phan et al., 2005; van Reekum et al., 2007). Collectively, these studies support a role for MPFC in generating and maintaining reappraisals in a manner that may often involve self-reflection.

DORSAL ANTERIOR CINGULATE CORTEX

Although early reports suggested that dACC activity is more associated with the performance of cognitive rather than emotional tasks (Bush, Luu, & Posner, 2000), it is now clear that it is involved in monitoring conflicts between competing responses regardless of whether they are cognitive or affective (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Ochsner et al., in press). This makes sense, given that dACC activity correlates with self-reported affective states that likely involve conflict, such as the social distress (Eisenberger, Lieberman, & Williams, 2003) elicited by rejection.

Conflict monitoring may be the essence of dACC activation during reappraisal as well. dACC activity has been associated with both the down-regulation (Ochsner, Ray, et al., 2004; Phan et al., 2005) and up-regulation (Ochsner, Ray, et al., 2004) of negative emotion in reappraisal studies. Activity in the dACC has also been shown to positively correlate with reappraisal success (Ochsner et al., 2002) and to vary inversely with self-reported intensity of negative emotion (Phan et al., 2005). These results suggest that dACC may monitor conflict flexibly in the service of a specific regulatory goal (if one is so instructed).

LATERAL ORBITOFRONTAL CORTEX

Prior research supports a role for OFC in flexibly selecting context-appropriate behaviors and emotions, with LOFC showing activation, for example, when a previously rewarded value has to be suppressed (Elliott, Dolan, & Frith, 2000). Both structurally and functionally, LOFC is similar to VLPFC. Several studies have implicated LOFC in down-regulating negative emotion (Goldin et al., 2008; Lévesque et al., 2003; Ochsner, Ray, et al., 2004; Phan et al., 2005). In particular, Lévesque and colleagues (2003) report a positive correlation between self-reported sadness and activation

of the right LOFC during emotion regulation, lending support to the idea that LOFC is important for guiding reappraisal.

Impact of Individual Differences on the Working Model

Careful study of individual differences in healthy populations may serve several purposes, particularly in the domain of emotion regulation. First, understanding stable individual differences may allow for a greater degree of experimental control that reduces noise in psychological and neuroscientific studies of emotion and emotion regulation. Second, increased investigations into basic connections between individual differences and emotional reactivity and regulation may increase opportunities for translational clinical research. This may both improve screening for individuals who may be at increased risk of developing psychopathology and help clarify connections between typical and atypical variation.

Because of space limitations and the fact that individual differences in the neural bases of emotion have been reviewed extensively elsewhere (Hamann & Canli, 2004), by way of illustration, we first briefly review two interrelated examples related to individual differences in amygdala activity. The first example concerns individual differences in trait rumination, which reflects a tendency to focus on negative emotions and negative aspects of the self (Nolen-Hoeksema, 2000). Ray and colleagues (2005) reported that greater trait rumination was correlated with greater recruitment of the amygdala when participants were asked to up-regulate their negative emotion via reappraisal and when participants were simply asked to view a negative stimulus. This suggests that the tendency to ruminate, which involves turning an event over and over again in one's mind, may depend on some of the same cognitive control systems as does reappraisal. Furthermore, it suggests that the tendency to ruminate "tunes" these systems so that they are able to more effectively down- or up-regulate the amygdala, depending on the reappraisal goal (Ray et al., 2005). These data importantly suggest that ruminators have the ability to effectively reappraise, but they may not know when to do so, or how. The second example concerns stable, trait-related individual differences in negative affect, which have been shown to be positively correlated with amygdala activation to negative pictures when participants were instructed to maintain their emotional response rather than passively view the picture (Schaefer et al., 2002). These data suggest that another factor—the tendency to experience negative affect in general—may in part be attributable to the ability to maintain activation of the amygdala during a negative event.

Another angle on individual differences is provided by the emerging field of imaging genetics, which offers insight into what lower level mechanisms might underlie differences in amygdala reactivity. Several researchers have reported an association between amygdala reactivity and a poly-

morphism in the human serotonin transporter gene (Munafo, Brown, & Hariri, 2008). The short allele of the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) has been associated with increased amygdala reactivity in response to fearful and angry faces (Hariri et al., 2005) and with increased diagnosable depression in response to stressful life events in a longitudinal study of a large, representative birth cohort (Caspi et al., 2003). The work reviewed in the prior paragraph suggests that these polymorphisms should also be related to the typical range of differences in factors that predispose healthy individuals to depression, such as rumination or trait negative affect. Although such relationships have yet to be examined, it is clear that genetic studies have the potential to further our understanding of how genes and environment interact to produce variance in clinical and nonclinical behavioral phenotypes.

Application of the Working Model to Psychopathology

Because characterizations of *dysfunctional* emotion regulation are only as good as the assumptions of *functional* (i.e., adaptive and effective) emotion regulation from which they are derived (Ochsner, 2008), until this point we have delayed an in-depth discussion of psychopathology. In this final section, we use our working model for the neural bases of typical emotion regulation to examine neuroimaging findings in clinical populations. In doing so, we offer broad hypotheses about brain-based abnormalities that contribute to emotional dysregulation across clinical disorders and also discuss current and future disorder-specific research endeavors. In the present review, we primarily focus on schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), and anxiety disorders (AD), including posttraumatic stress disorder (PTSD). Our decision to include these four disorders was based on their prevalence in the general population, their relevance to emotional appraisal and reappraisal, and also their coverage in the neuroimaging literature.

Functional Neuroimaging in Clinical Populations

Although this section focuses primarily on functional brain differences associated with clinical disorders, it is important to acknowledge two additional factors that might influence both behavior and the results of brain imaging studies.

Implications of Brain Structure

The first factor is structural brain changes that are found in many psychopathological populations. For example, one study found that people with schizophrenia who were also violent exhibited reductions in whole brain

volume (Barkataki, Kumari, Das, Taylor, & Sharma, 2006), while others showed localized abnormalities in regions associated with emotion generation and regulation. In like fashion, decreased amygdala volumes are seen in BD (Rosso et al., 2007), PTSD (Karl et al., 2006), unmedicated MDD (Hamilton, Siemer, & Gotlib, 2008), and AD (Milham et al., 2005). Diminished volumes are also noted in regions associated with emotion regulation, such as ventral and lateral portions of the PFC in BD (Adler, Levine, DelBello, & Strakowski, 2005; Lyoo et al., 2004) and the OFC and PFC in MDD (Bremner, 2005). Although the intricacies of structure–function relationships are still being worked out, for present purposes, when interpreting functional brain data, we assume that to the degree structural abnormalities exist there will be functional impairment, but that when functional abnormalities exist they may or may not arise from structural changes.

Medication and Neuroimaging

In recent years, BOLD fMRI has become an increasingly popular tool for investigating brain activity in psychopathological populations. Implicit in this work is the assumption that the BOLD signal is a reliable and constant indicator of brain activity. Although it is unclear how or whether psychotropic medications modulate the BOLD signal, other chemical agents ranging from caffeine (Laurienti et al., 2002) to opioids (Leppa et al., 2006) significantly affect BOLD responses. Additionally, common psychiatric medications like lithium (Foland et al., 2008) and neuroleptics (Lieberman et al., 2005) may alter brain morphology. Again, it is important to consider these findings when interpreting results among psychiatric patients who vary in their current or historical medication usage. Our incomplete understanding of medications' effects on neuroimaging data leads us to acknowledge that medications may impact findings, although it remains unclear the extent to which or how medications may do so.

Hypotheses and Research Questions

Earlier in this chapter, we outlined a model rooted in the reappraisal literature wherein one class of brain structures was described as sources of emotion regulatory processes (LPFC, MPFC, dACC, LOFC) and another class as appraisal regions that are targeted by those processes (amygdala, insula, striatum, MOFC). In this model, rises in emotion are correlated with enhanced activity in appraisal structures (e.g., amygdala), while the attenuation of emotion is associated with reduced activity in these structures coupled with increased activity in reappraisal structures (e.g., LPFC). Thus, by comparing patterns of hypo- and hyperactivations within and between appraisal and reappraisal systems in healthy and clinical popula-

tions, we can draw inferences about the mechanisms that might mediate dysfunction in those disorders.

By way of illustration, suppose that individuals with MDD exhibit amygdala hyperactivity during anticipation of an aversive stimulus but hypoactive ventral striatal activity during a reward-learning paradigm. Such results would suggest that individuals with MDD perhaps too readily form predictions and appraisals about negative stimuli but underrespond to positive stimuli. Now consider a scenario where both appraisal and reappraisal regions are involved. For example, if PTSD were associated with excessive amygdala activity but typical dACC responses to traumatic images, this suggests that dysfunction during appraisal rather than reappraisal contributes to abnormal emotional responses associated with the disorder. If aberrant responses were seen in both sets of brain regions (as, in fact, is the case in PTSD; Etkin & Wager, 2007), however, we might infer that enhanced activity in the amygdala was supporting a heightened tendency to perceive threat and that hypoactivity in the dACC was indicative of a reduced capacity to monitor unwanted emotional states during reappraisal.

When interpreting neuroimaging data on emotion generation and regulation in psychopathology, two additional issues should be noted. First, patients can show a range of responses to different kinds of "emotional" stimuli, with patterns of abnormal appraisal reflecting either stimulus-specific or stimulus-generic patterns of dysfunction (e.g., a person with spider phobia may respond abnormally only to spider images but not to other aversive images). Thus, it is critical to consider the "fit" of a stimulus with a given disorder. Second, in the absence of an instructed regulation condition, it is impossible to know whether any given emotional response was "unregulated" or whether participants spontaneously regulated it in idiosyncratic ways. This means that results associated with "free viewing" or uninstructed response paradigms are fundamentally ambiguous. This may be particularly relevant if there are specific regulation strategies that some clinical groups tend to use spontaneously that differ from those of healthy populations (e.g., if individuals with MDD tend to self-distract and healthy controls do not). That said, we now move forward to a review of current perspectives on the neural mechanisms of emotion regulation in various clinical disorders.

Schizophrenia

In the emotional domain, schizophrenia is characterized by reduced emotional expressivity (Kring & Moran, 2008) and an impaired ability to perceive emotions in others (Kohler & Martin, 2006). Despite these impairments in emotional expression and perception, it has been strongly suggested that individuals with schizophrenia experience typical to exces-

sive amounts of emotion (Kring & Moran, 2008; Myin-Germeys, Delespaul, & deVries, 2000), albeit in ways that qualitatively differ from healthy controls (Cohen & Minor, in press). These affective abnormalities bring into question whether individuals with schizophrenia falter in their appraisals of emotionally evocative stimuli, their regulation of these appraisals, or both. In support of the impaired appraisal possibility, individuals with schizophrenia show reduced striatal activity compared with healthy controls in response to cues signifying potential reward (Juckel et al., 2006). Hypoactivity in the ventral striatum could underlie improper appraisals of positive stimuli and anhedonia, but it could also mean that individuals with schizophrenia fail to *anticipate* enjoying a reward but do not necessarily fail to find a reward pleasurable upon receipt (Gard, Kring, Gard, Horan, & Green, 2007). Diminished amygdala responses to negative stimuli (e.g., sad faces, aversive scenes) have also been observed in individuals with schizophrenia (Takahashi et al., 2004; Williams et al., 2004), as has reduced anterior insula activity in response to disgusted faces (Phillips et al., 1999). Thus, observations of reduced activity across appraisal regions in the brain have been associated with a failure to properly perceive, learn, and respond to positive and negative emotional stimuli in schizophrenia. Future studies may wish to investigate, however, whether such hypoactivity occurs in tasks that do not involve emotion perception (e.g., emotion induction).

Cognitive control deficits shown by individuals with schizophrenia appear linked to abnormal brain activity in regions associated with generating and maintaining reappraisals, such as the dACC, MPFC, and DLPFC (Kerns, Nuechterlein, Braver, & Barch, 2008). Interestingly, individuals with schizophrenia exhibit abnormal correlations in activity between the amygdala and the ACC/MPFC when viewing emotional faces (Das et al., 2007), which suggests dysfunctional dynamics between sources and targets of emotion regulation typically observed in reappraisal paradigms. One recent study found that individuals with schizophrenia recruit the DLPFC more strongly than controls and do not deactivate emotion generation circuitry when classifying affective stimuli in the presence of incongruent affective distracters (Park, Park, Chun, Kim, & Kim, 2008). These results were interpreted as evidence for individuals with schizophrenia exerting more cognitive effort (DLPFC hyperactivation), yet, according to behavioral results, failing to inhibit responses to task-irrelevant affective information. To date, no functional imaging studies have examined effortful emotion regulation in schizophrenia. Individuals with schizophrenia report utilizing reappraisal and suppression to regulate their emotions (Henry, Rendell, Green, McDonald, & O'Donnell, 2008), however, and a recent behavioral study found them capable of down-regulating emotional responses to amusing film clips (notably, patients failed to amplify their responses) (Henry et al., 2007). Whether individuals with schizophrenia

could effectively down-regulate negative emotional responses and whether abnormal PFC activity would be observed during such regulation has yet to be explored.

Bipolar Disorder

BD is an affective disorder characterized by at least one lifetime episode of mania. Most people with BD also experience episodes of depression. Both mania and depression include symptoms of severe emotional dysregulation. With respect to the appraisal versus reappraisal equation, most of our knowledge about the neural bases of emotion regulation in BD comes from studies examining perception of emotional faces. Although faces do not elicit strong emotional responses, it is generally believed that the basic processes involved in deciding facial emotion are similar to those involved in appraising other emotional stimuli. That being said, studies of emotion perception generally suggest that individuals with BD exhibit broad impairments in appraisal processes. For example, BD is associated with deficits (e.g., slower RTs and reduced accuracy) in identifying (Malhi et al., 2007; Yurgelun-Todd et al., 2000) and recalling (Dickstein et al., 2007) emotional faces, and these tendencies may be associated with their degree of social-emotional dysfunction. Strikingly, these behavioral deficits are not accompanied by diminished activity in brain systems associated with appraisal but greater activity in them: When viewing emotional faces, individuals with BD exhibit exaggerated activity in structures typically associated with emotional identification and learning like the amygdala and striatum (Lawrence et al., 2004; Yurgelun-Todd et al., 2000).

At present, the meaning of this relative hyperactivity is not yet clear, and there are at least two questions about what it might reflect. The first is whether the hyperactivity observed is compensatory or reflects a general dysfunction of appraisal systems. In favor of compensation, it has been shown that individuals with BD show impaired overall memory for emotional faces but are more likely to recall faces that evoked relatively hyperactive dorsal striatal responses during encoding (Dickstein et al., 2007). This suggests that hyperactivity in appraisal areas may reflect attempts to compensate for overall poor performance in tasks involving emotion detection and memory by enhancing processing of, and thereby activation to, specific subsets of stimuli. In favor of general dysfunction, however, is the fact that people with BD, whether depressed or manic, exhibit elevated ventral striatum activity not just to negative emotional faces (Chen et al., 2006) but also at rest and in nonemotional attention tasks as well (Keener & Phillips, 2007).

The second question is whether heightened responses in appraisal systems relate to the cyclical shift between episodes of mania and depression that tend to recur across the lifespan for individuals with BD. Current data

suggest that such variation does exist and that how it varies depends on the valence of the emotional stimulus. On one hand, individuals with BD who are currently depressed consistently show enhanced striatal and amygdala responses to positive and negative stimuli across tasks that demand differential levels of attention or cognitive processes (Chen et al., 2006; Lawrence et al., 2004; Malhi et al., 2004). On the other hand, those in the manic phase of BD show *diminished* striatal and amygdala responses to positive stimuli (Chen et al., 2006; Malhi et al., 2004) and variable amygdala responses to negative emotional stimuli. In paradigms that require individuals with mania to cognitively label a negative emotional expression or evaluate its intensity, participants often show attenuated amygdala responses (Chen et al., 2006; Lennox, Jacob, Calder, Lupson, & Bullmore, 2004), whereas those that present emotional stimuli in a task-irrelevant way or that ask participants to perform a task that does not directly relate to a stimulus's affective content (e.g., color discrimination) tend to report enhanced amgydala and insular responses (Chen et al., 2006; Elliott et al., 2004).

Taken together, these data are interesting in two respects. First, they suggest a relationship between MDD (see later discussion) and the different phases of BD: Individuals in the manic phase of BD show neural responses to positive stimuli similar to those exhibited by individuals with MDD, whereas individuals in the depressed phase of BD show responses to negative stimuli like those exhibited by individuals with MDD. This pattern could potentially be used to develop more accurate means for differentiating unipolar and bipolar depression (Keener & Phillips, 2007). Second, these data suggest that during the manic phase of BD the response of appraisal systems is more subject to cognitive modulation than it is during the depressed phase. This conclusion is limited, however, by the fact that only attentional deployment paradigms have been used to test this hypothesis.

Although no studies have directly examined reappraisal in BD, abnormal neural responses have been observed in brain regions that support reappraisal during various emotion and cognitive control tasks. For example, a number of emotion perception studies have reported individuals with BD exhibiting abnormal activity in the LPFC, MPFC, and the ACC in response to emotionally expressive faces (Chen et al., 2006; Lawrence et al., 2004). Additionally, patterns of hyperactivation across the PFC have been observed in executive function tasks in BD (Brambilla, Glahn, Balestrieri, & Soares, 2005). A handful of studies have used paradigms where participants must respond to task-relevant stimuli while exerting cognitive control to ignore task-irrelevant stimuli that may contain affective content. Findings from these studies have produced inconsistent results. On the one hand, making nonaffective assessments of affective stimuli has been shown to elicit reduced activity in lateral and medial portions of the PFC associated with regulating emotion (Lagopoulos & Malhi, 2007; Malhi,

Lagopoulos, Sachdev, Ivanovski, & Shnier, 2005) in individuals with BD. On the other hand, inhibiting responses to task-irrelevant or incompatible affective information appears to evoke enhanced activity in the LPFC and MPFC (Elliott et al., 2004) as well as a dACC region that may resolve interference between appraisals and response tendencies (Wessa et al., 2007). Future research in BD may seek to compare neural responses associated with cognitive change strategies like reappraisal to those evoked by the attentional deployment paradigms described previously. Such endeavors would clarify whether BD is marked by dysfunction in appraisal, reappraisal, or both.

Major Depressive Disorder

MDD is characterized by prolonged dysphoric mood as well as disrupted motivation, thought, and behavior. Whether tendencies among individuals with MDD to attend and respond to the negative is due to a bottom-up enhancement of negative stimuli or an impaired top-down regulatory ability is uncertain because few studies have been designed to tease apart these processes.

For example, it has been shown that individuals with MDD (1) exhibit abnormal cerebral blood flow and glucose metabolism in the amygdala, insula, striatum, and OFC as well as in the LPFC and MPFC during uninstructed "resting" conditions (Drevets, 2000); (2) show overall diminished neural activity to happy faces (Lawrence et al., 2004; Surguladze et al., 2005); (3) show enhanced striatal and amygdala responses to sad faces (Elliott et al., 2004; Surguladze et al., 2005); and (4) show sustained amygdala reactivity to emotional words (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Although these findings suggest that negative affective information is preferentially detected and processed over positive affective information in subcortical appraisal regions in MDD, whether these observations reflect differences in reactivity or regulation is not clear. Also unclear is how amygdala reactivity to negative emotional stimuli relates to well-being; although some studies have found responsivity to positively correlate with symptom severity (Lee et al., 2007), others suggest it predicts better longitudinal outcomes (Canli et al., 2005).

Abnormal activity (particularly a lack of left lateralized activity) in the DLPFC, a brain region associated with the control processes supporting reappraisal, has also been linked to emotion dysregulation in MDD. On one hand, when healthy controls make valence judgments about emotional stimuli, they show a rise in activity in the left DLPFC that corresponds to how negative they perceive stimuli to be (Grimm et al., 2008). On the other hand, individuals with MDD exhibit hypoactivity in the left DLPFC that correlates *positively* with stimuli valence as well as hyperactivity in the right DLPFC that is associated with depression symptoms. These findings suggest that an absence of left lateralized PFC activity and the presence

of right LPFC hyperactivity in response to negative emotional stimuli in MDD may be linked to inappropriate responding, ineffective spontaneous emotion regulation, or both.

At present, only two studies have examined the neural mechanisms of cognitive reappraisal in MDD. In one of these studies, healthy controls were found to only activate the left LPFC during down-regulation of negative emotion, while individuals with MDD activated bilateral LPFC (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). This pattern of right LPFC activity during instructed regulation mirrors what was found previously during an emotion judgment task. Results from another study suggest that individuals with MDD also differ from healthy controls in that efforts to down-regulate their emotions seem to enhance, rather than diminish, amygdala and insula activity (Beauregard, Paquette, & Lévesque, 2006). This may be because left LPFC activity attenuates amygdala activity via the ventral MPFC during reappraisal in healthy controls, but in MDD this mediating effect is absent and instead the amygdala and ventral MPFC are coactivated (Johnstone et al., 2007). According to results from the Beauregard study, this activity in the amygdala and MPFC is strongly associated with the degree of difficulty experienced during down-regulation for individuals with MDD. This could mean that individuals with MDD are less successful at regulating and thus exhibit enhanced activity in areas associated with emotion perception and self-reflection. Alternatively, participants with MDD could show overall enhanced neural activity as a result of compensatory attempts at down-regulation. Future attempts to characterize voluntary emotion regulation in MDD may be enhanced by collecting in-scanner affect ratings. Doing so would build bridges between behavioral and neural responses associated with voluntary emotion regulation in MDD and would also give greater insight into whether individuals with MDD differ from healthy controls in their effectiveness at using reappraisal. MDD researchers may additionally wish to clarify how baseline reactivity to negative emotional stimuli may predict treatment outcome and how treatment might modify neural responses in voluntary emotion regulation paradigms.

Anxiety Disorders

Anxiety, as a state, may be described as agitation or arousal caused by the perception of a real or imagined threat (Amstadter, 2008). In AD, this anxious state is chronically activated by specific (e.g., social anxiety disorder [SAD], specific phobias, and PTSD) or varied (e.g., generalized anxiety disorder [GAD]) triggers. Within the context of our model of emotion regulation, AD may represent an inability to accurately appraise what is threatening, an inability to reappraise threat, or both.

In support of the appraisal possibility, the insula and amygdala consistently hyperactivate in response to negative or threatening stimuli in

SAD and specific phobias and often in PTSD as well (Etkin & Wager, 2007). These hyperactivations have been observed in response to negative emotional facial expressions (Blair et al., 2008; Evans et al., 2008) as well as a speech preparation task (Lorberbaum et al., 2004) in individuals with SAD, to trauma-themed pictures and scripts for PTSD patients (Shin et al., 2004; Whalley, Rugg, Smith, Dolan, & Brewin, 2009), and to photographs of spiders for people with spider phobia (Straube, Mentzel, & Miltner, 2006). GAD is unusual in its lack of specificity for what produces anxious feelings, and it is perhaps for this reason that some neuroimaging studies have not found anxiety or fear-inducing stimuli to activate the amygdala (Blair et al., 2008), whereas others have found it to hyperactivate the amygdala (McClure et al., 2007) in individuals with GAD. In summary, inappropriate threat appraisals in AD appear linked to abnormal activity in structures involved in perceiving, responding to, and remembering fear-inducing stimuli, such as the amygdala and insula (Etkin & Wager, 2007).

In addition to the hyperactivations observed in targets of emotion regulation described previously, a number of functional abnormalities in individuals with AD have been noted in control regions associated with emotion regulation. In contrast to healthy controls, individuals with SAD exhibit enhanced right LOFC activity—associated with the down-regulation of negative emotion—in response to angry voices (Quadflieg, Mohr, Mentzel, Miltner, & Straube, 2008). SAD is also associated with enhanced rostral (Amir et al., 2005; Blair et al., 2008) and dorsal (Phan, Fitzgerald, Nathan, & Tancer, 2006) ACC activity during viewing of angry, disgusted, and fearful faces. Such ACC activity may be evidence of enhanced monitoring of negative social cues in SAD. In contrast to other negative facial expressions, fearful faces seem unique in their recruitment of lateral and medial PFC regions among individuals with SAD (Blair et al., 2008). LPFC responses to fearful face stimuli in SAD are strongly correlated with anxiety symptoms and, interestingly, are not observed in GAD, thus suggesting a functional means for differentiating the two disorders (Blair et al., 2008). Individuals with specific phobias exhibit similar hyperactivations in the LOFC (Dilger et al., 2003) as well as dorsal MPFC and dACC (Straube et al., 2006) but not typically in the LPFC when viewing phobia-related stimuli. ACC and dorsal MPFC hyperactivations in people with specific phobias are lessened by a demanding task, whereas amygdala activity is not. This suggests that fast, automatic subcortical appraisals of threat may not be attenuated by distraction but that more deliberative ones generated in the cortex may be (Straube et al., 2006). On this view, PFC hyperactivation may reflect efforts to regulate behavior when perceiving threat or elaborate processing of threatening information. Interestingly, the negative correlation in activity between these frontal regions and amygdala activity that is observed in healthy controls is dampened (Monk et al., 2008) or even positive (McClure et al., 2007) in AD, and positive correlations are linked to poorer treatment outcomes (Whalen et al., 2008).

Unlike those with other AD, individuals with PTSD exhibit hypoactivity in the dACC and ventral MPFC and an *inverse* relationship between the amygdala and MPFC regions (Etkin & Wager, 2007). MPFC hypoactivity has been implicated in reduced emotional awareness (Frewen et al., 2008) and suggests that PTSD pathology extends beyond an exaggerated fear response (Etkin & Wager, 2007).

In healthy adults, using strategies like "reality checking" to regulate state anxiety elicits enhanced activity in the LPFC, MPFC and dACC and diminished activity in the amygdala and insula (Herwig et al., 2007). Self-distraction during the anxious anticipation of shock may evoke tonic activity in the left LPFC (Kalisch, Wiech, Herrmann, & Dolan, 2006). What patterns of activity individuals with AD might elicit during voluntary emotion regulation is unclear, however. Amygdala responses to disorder-specific stimuli occur more quickly than to other types of stimuli (Larson et al., 2006) and persist even when attentional resources are low (Straube et al., 2006). For these reasons, effortful emotion regulation would be unlikely to affect initial appraisals but might successfully shape reappraisals. It would be informative to explore whether strategies like reappraisal attenuate or enhance hyperactivation in regions associated with emotion regulation during exposure to threat for individuals with AD. Knowing this might clarify whether frontal activity observed in paradigms without a regulation instruction are due to efforts at spontaneous regulation, higher level processing of threat stimuli, extended vigilance, or something else entirely.

Conclusions and Future Directions

This chapter has sought to provide an overview of neuroscientific investigations into emotion and emotion regulation, with a particular focus on describing evidence for a working model of the functional architecture of emotion regulation that can be applied to understanding mechanisms of dysfunction in clinical disorders. In so doing, we have focused on describing which neural structures have been shown to be consistently active during cognitive reappraisal in healthy individuals (i.e., LPFC, MPFC, dACC, LOFC), and have noted which neural structures implicated in emotional appraisal are often modulated during reappraisal (i.e., amygdala, insula, striatum, MOFC). In applying this model to understanding psychopathology, we found qualified support for our hypothesis that clinical disorders involve abnormal activation of emotional appraisal systems, abnormal activation of cognitive control mechanisms (e.g., reappraisal mechanisms), or both. This support is tempered by the lack of published data using true reappraisal paradigms in many forms of psychopathology.

Future research may involve investigating how patients compare with healthy controls as well as other clinical groups in reappraisal paradigms. These endeavors might be most fruitful when they involve the concurrent

collection of self-reported emotional experience data, psychophysiological responses, and functional and structural brain data. This knowledge of how healthy patterns of brain activation compare with activation in psychopathology, along with increased knowledge of how salient nonclinical individual differences affect brain activation, may increase our ability to screen individuals for psychopathology and predict treatment outcomes while simultaneously furthering our understanding of the neural loci that are most crucial for emotion regulation.

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