CHAPTER 3

Neural Bases of Emotion Regulation in Nonhuman Primates and Humans

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One of the most important characteristics that distinguish between humans and other species is our capacity to regulate our emotions. Emotion regulation clearly reaches its pinnacle in humans. This capacity provides important flexibility to our behavioral repertoire and it also confers significant risk (see, e.g., Davidson, Putnam, & Larson, 2000c). More than any other species, our emotional reactions are under some degree of voluntary control. However, it appears that the same substrate that confers this flexible competence also can become dysfunctional and lead to abnormalities of emotional regulation that can result in psychopathology. Many psychiatric disorders in humans involve abnormalities in our emotion regulatory skills, and it is likely that the naturally occurring incidence of such pathology is greater in humans than in other species, in part because of our increased capacity to regulate our emotions. Notwithstanding these important species differences, the study of nonhuman primates clearly provides us with an important and powerful window to study some of the basic neural substrates of emotion regulation. And as we note below, there are certain components of emotion regulation that can be more crisply examined in an animal model and that shed important new light on issues that have been difficult to empirically address in the study of emotion regulation in humans. The study of the nonhuman primate we would argue is essential in furthering our understanding of emotion regulation because it sits between rodent models and human studies. Rodent models have provided powerful new data on the molecular machinery underlying some aspects of emotion regulation (e.g., Rumpel, LeDoux, Zador, & Malinow, 2005). However, the prefrontal cortical territories and the amygdala of the rodent are anatomically distinct from the primate and argue for the need to develop a primate model that has a prefrontal cortex that more closely resembles what we have in humans (see, e.g., Stefanacci & Amaral, 2002).

Our work on emotion regulation in both humans and nonhuman primates has emphasized the important role of individual differences. In many prior publications, we have suggested that affective style or individual differences in the subcomponents of emotional reactivity, are importantly determined by variations in emotion regulation (see, e.g., Davidson, 2000a; Davidson, Jackson, & Kalin, 2000a). We have suggested that many features of affective style are in fact determined by individual differences in emotion regulation and thus it is critical to develop a better and more complete understanding of individual differences in emotion regulation to enable us to understand affective style.

Elsewhere in this handbook (Gross & Thompson, this volume) the many varieties of emotion regulation are described. One continuum along which emotion regulation varies is from fully automatic and nonconscious to voluntary, effortful, and conscious processing. Gross and Thompson (this volume) also call attention to *intrinsic* and *extrinsic* forms of emotion regulation. The former refers to strictly internal influences on emotion regulation within the individual while the latter refers to social and contextual influences that serve to regulate emotion. We have devoted considerable attention to developing experimental paradigms to probe both automatic and voluntary emotion regulation in humans (see, e.g., Jackson, Malmstadt, Larson, & Davidson, 2000; Jackson et al., 2003; Urry et al., 2006). In our nonhuman studies we have emphasized *extrinsic* influences on emotion regulation, in part because such influences are likely more significant than *intrinsic* influences in nonhuman primates and, second, because they are readily amenable to experimental manipulation.

This chapter begins with a brief summary of some of the key components of the neural circuitry of emotion and emotion regulation, drawing on a broad literature including human and nonhuman studies. After the circuitry of emotion- regulation is described, we then focus on key issues in the study of the neural bases of emotion regulation in nonhuman primates with an emphasis on the contextual regulation of emotion.

A SELECTIVE REVIEW OF KEY NEURAL CIRCUITRY FOR EMOTION AND EMOTION REGULATION

In many recent publications Davidson and colleagues (e.g., Davidson, 2000a, 2000b, 2004a, 2004b; Davidson, Jackson, et al., 2000), have suggested, along with others that emotions serve to facilitate adaptive behavior and decision making in response to salient events. Emotions that are poorly regulated and/or occur out of context can impair functioning. Over the past decade, tremendous progress has been made in delineating the neural circuitry of emotion and more recently, emotion regulation. What is particularly gratifying about these developments is the convergence that is occurring between basic research at the animal level and translational research at the human level. We have proposed that individual differences in emotion regulation are fundamental to understanding variations in affective style (Davidson, 2000a, 2004a). Moreover, we have also suggested that abnormalities especially in the capacity to downregulate negative affect, but perhaps also in the capacity to upregulate, maintain and enhance positive affect, are crucial in determining vulnerability to psychopathology, particularly mood and anxiety disorders. In this brief section, we review some of the key pertinent findings in the literature to set the stage for our own program of research that is reviewed in more detail in the subsequent section.

Neural Circuitry of Emotion

Affective neuroscience (Davidson & Sutton, 1995) refers to the study of the neural substrates of emotion-relevant processes that underlie emotional reactivity, emotion regulation, and other emotion-relevant subcomponents. Work in this area, relying on animal models, lesion studies, and electrophysiological and neuroimaging studies has identified a number of key structures that together form the brain's emotion circuitry, structures that include dorsolateral and ventral regions of prefrontal cortex (including the anterior cingulate cortex [ACC]), amygdala, hippocampus, and insula (see, e.g., Davidson, 2000b). Here we focus primarily on prefrontal cortex and amygdala because these components are most pertinent to our research, though we make selective references to other key structures in this circuitry.

Prefrontal Cortex

Although the prefrontal cortex (PFC) is often considered to be the province of higher cognitive control, it has also consistently been linked to various features of affective processing (see, e.g., Nauta, 1971, for an early preview). Miller and Cohen (2001) have recently outlined a comprehensive theory of prefrontal function based on nonhuman primate anatomical and neurophysiological studies, human neuroimaging findings and computational modeling. The core feature of their model holds that the PFC maintains the representation of goals and the means to achieve them. Particularly in situations that are ambiguous, the PFC sends bias signals to other areas of the brain to facilitate the expression of task-appropriate responses in the face of competition with potentially stronger alternatives. If a signal of competition emerges, this output signals the need for controlled processing. The dorsolateral PFC (Brodmann's area [BA] 9 and 46) is assumed to be critical for this form of controlled processing, in that it represents and maintains task demands necessary for such control and inhibits (see, e.g., Garavan, Ross, & Stein, 1999) or increases neural activity in brain regions implicated in the competition. The most rostral zone of the PFC, the frontopolar region or rostral PFC (BA 10), has been identified specifically as subserving a system that somehow weights the priority between internally generated, stimulus-independent thought versus stimulus-oriented thought or current sensory input (see, e.g., Burgess, Simons, Bumontheil, & Gilbert, 2005). Because voluntary emotion regulation clearly represents a balance between internally generated versus externally elicited processing, it is likely that BA 10 will be involved. Interestingly, BA 10 is the zone of PFC that shows the greatest increase in size across primate species with humans showing the largest relative size (relative to the remainder of the brain) compared with apes (Semendeferi, Armstrong, Schleicher, Ziles, & Van Hoesen, 2001). The structure that has been implicated in monitoring is a region of medial PFC called the ACC, which some have proposed acts as a bridge between attention and emotion (Devinsky, Morrell, & Vogt, 1995; Vogt, Nimchinsky, Vogt, & Hof, 1995; Ebert & Ebmeier, 1996; Mayberg et al., 1997).

Amygdala

Although a link between amygdala activity and negative affect has been a prevalent view in the literature, particularly when examined in response to exteroceptive aversive stimuli (e.g., LeDoux, 2000), recent findings from invasive animal studies and human lesion and functional neuroimaging studies are converging on a broader view that regards the amygdala's role in negative affect as a special case of its more general role in directing attention to affectively salient stimuli and issuing a call for further processing of stimuli that have major significance for the individual. Extant evidence is consistent with the argument that the amygdala is critical for recruiting and coordinating cortical arousal and vigilant attention for optimizing sensory and perceptual processing of stimuli associated with underdetermined contingencies, such as novel, "surprising," or "ambiguous" stimuli (Whalen, 1998; Holland & Gallagher, 1999; see also Davis & Whalen, 2001). Most, though not all, stimuli in this class may be conceptualized as having an aversive valence as we tend to have a negativity bias in the face of uncertainty (Taylor, 1991), though at least parts of the amygdala have also been implicated in appetitive processes (Holland & Gallagher, 1999). Importantly, by way of the central nucleus, the amygdala contributes to mobilization of behavioral, autonomic, and endocrine outputs (LeDoux, 2000). Additional detail regarding the contribution of the amydala to individual differences in aspects of emotion regulation are provided below.

Neural Correlates of Regulation and Dysregulation

An important component of disorders of emotion that was highlighted in a National Institute of Mental Health report on the neural and behavioral substrates of mood and mood regulation is abnormalities in the regulation of emotion (Davidson et al., 2002a). We (e.g., Davidson et al., 2000a, 2000b) and others (e.g., Ochsner & Gross, 2005) have proposed that prefrontal activity may be particularly important for emotion regulation and in some of our work, we have found that individuals with high levels of baseline left-prefrontal activation in particular (as assessed with electrophysiological methods) are particularly skilled in the downregulation of negative affect. The correlates of individual differences in asymmetric prefrontal function may derive at least in part from a fundamental difference in the capacity to regulate negative affect, differences that appear to be consequential for positive psychological adaptation (Urry et al., 2004a). According to this formulation, subjects with relative hypoactivation of left prefrontal function may be impaired in the ability to regulate negative affect (Jackson et al., 2003). While this electrophysiological work provides important and cost-effective information about regional cortical contributions to emotion regulation, the spatial resolution of these scalp-recorded signals is relatively coarse. To date, only a handful of studies using measures with high spatial resolution, such as functional, magnetic resonance imaging (fMRI), have been reported (Beauregard, Levesque, & Bourgouin, 2001; Schaefer et al., 2002; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Levesque et al., 2003; see review in Ochsner & Gross, 2005).

In one of the first studies of its kind, Schaefer et al. (2002) performed an fMRI study in which participants were instructed to regulate ("maintain" or "passive") negative affect in response to pictures. As hypothesized, results showed greater amygdala activation while subjects were maintaining their negative emotion compared to when they were passively experiencing negative affect. Using an adapted version of the Jackson et al. (2000) paradigm, Ochsner et al. (2002) asked participants to reinterpret negative photos such that their negative response was diminished in one condition ("reappraise"), and to pay attention to but not to modify their feelings in any way ("attend") in another condition. Supporting the prediction that regulation of negative affect should draw on brain regions implicated in cognitive control, they found that voluntarily reducing negative affect was associated with activation in the left superior, middle, and inferior frontal gyri and dorsomedial PFC. They also found reduced signal in the left medial orbital frontal cortex and the right amygdala, suggesting that these regions are sensitive to reductions in unpleasantness or significance arising in the wake of regulatory efforts. Finally, they found that subjects with higher activation of dorsal ACC were more successful at reducing negative affect as measured via subjective ratings. More recently, Ochsner et al. (2004) reported on the effects of both increasing and decreasing negative affect. Compared to control trials in which subjects simply responded naturally, increasing and decreasing negative affect evoked greater activation in numerous frontal regions, including dorsal and ventral lateral PFC, dorsal medial PFC, and dorsal ACC. In addition, the amygdala tracked changes in affect, such that subject-initiated increases in negative affect resulted in greater left amygdalar activation relative to a control condition and decreases with less activation. In one of the few studies examining the neural correlates of regulating positive affect, Beauregard et al. (2001) found that males, instructed to inhibit sexual arousal by taking the perspective of a detached observer and distancing oneself in response to erotic film clips, produced activation in the right superior frontal (SFG; BA 10), left inferior frontal (IFG; BA 44), and right anterior cingulate (BA 32) gyri. In a second study, this group (Levesque et al., 2003) found that females suppressing sadness displayed activation in the right dorsolateral PFC (BA9), right orbitofrontal cortex (OFC; BA 47), and left IFG (BA 44).

More recently, we (Urry et al., 2006) have adapted a more faithful replica of the Jackson et al. (2000) for the scanner to interrogate the circuitry associated with the down-regulation of negative affect specifically. In this experiment, negative and neutral stimuli were presented. In response to negative pictures, subjects were randomly presented with instructions to enhance, suppress, or maintain their emotional response using cognitive reappraisal strategies that were taught to them in a preexperimental practice session. In response to the neutral pictures, subjects always received the instruction to maintain. A total of 17 participants between the ages of 63–66 years were tested.

We measured pupillometry in the scanner in order to provide a continuous realtime measure of autonomic activation that is generally thought to reflect "cognitive effort" (e.g., Tursky, Shapiro, Crider, & Kahnman, 1969). We wanted to establish that there were not differences in effort between the Enhance and Suppress conditions. If such differences did exist, then at least some of the difference between these conditions in levels of magnetic resonance (MR) signal change could be attributed to differences in effort. The pupillometry data reveals that both the Enhance and Suppress conditions produce comparable and significantly larger changes in pupil diameter compared with the Maintain condition. These findings indicate that there were not any major differences in effort between our critical emotion regulation conditions.

Our first major question was to determine whether the downregulation results in decreased BOLD signal in the amygdala relative to the Maintain condition and whether the Enhance condition leads to an increase in BOLD signal in the amygdala relative to the Maintain condition. Figure 3.1 presents the main effects for the left and right amygdalae for the condition contrast (Enhance, Suppress, Maintain) and reveals a reliable change in MR signal in the amygdala as a function of regulation instruction.

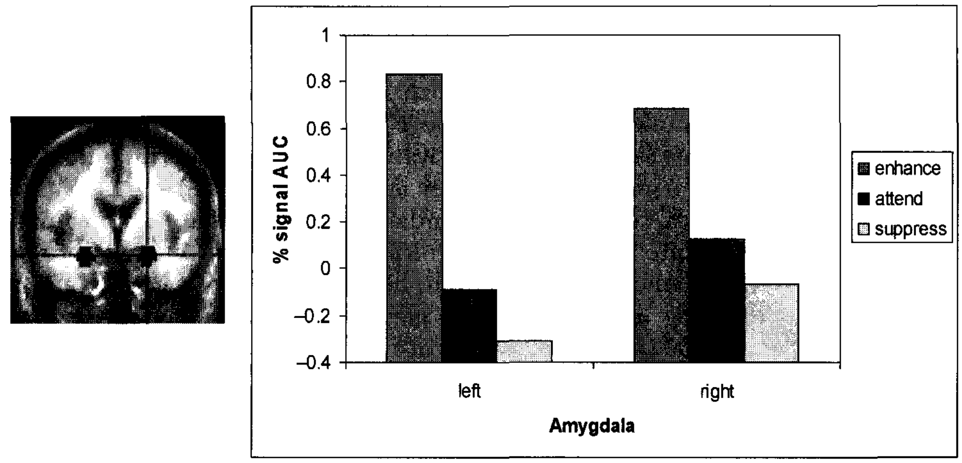

FIGURE 3.1. Amygdala regions of interest and signal change in response to the three regulation conditions during the presentation of negative pictures. Data from Urry et al. (2006).

Although we obtained a main effect for regulation condition on amygdala activation, there was considerable variation in the magnitude of amygdala signal reduction during the downregulate condition (compared with the Maintain condition). To better understand this variation, we asked what other regions of the brain are activated when subjects downregulate negative affect. This analysis was performed across subjects to enable us to address the nature and correlates of the individual differences in facility at downregulation of the amygdala.

We determined which areas of the brain were reciprocally coupled to signal change in the amygdala. The results of this analysis revealed a large and significant bilateral cluster in ventromedial prefrontal cortex (vmPFC) as displayed in Figure 3.2. These data indicate that subjects who show greater reductions in amygdala activation in response to the Suppress compared with the Maintain conditions show greater activation in the vmPFC prefrontal cortex during these respective conditions.

We next asked whether individual differences in amygdala and vmPFC signal change during instructed downregulation of negative affect predict another regulatory process that occurs in everyday life. Specifically, we asked whether the individual differences in MR signal change we observed were related to individual differences in the diurnal slope of cortisol. This question was of interest in light of other evidence indicating that subjects with flatter cortisol profiles (primarily contributed by higher cortisol values late in the day) do worse on a variety of outcomes (Abercrombie et al., 2004). In the week following the scan, subjects provided six saliva samples each day for 7 consecutive days. Our assay method employed the Salimetrics (State College, PA) cortisol enzyme immunoassay (EIA) kit. In light of prior data on the functional significance of individual differences in cortisol slope, we specifically focused on relations between MR signal change in the Suppress versus Maintain conditions. We predicted that those subjects who are relatively less able to decrease signal in the amygdala during the Suppress versus Maintain conditions should have a flatter cortisol slope. As Figure 3.3 reveals, those subjects who showed the smallest decrease in MR signal change in the

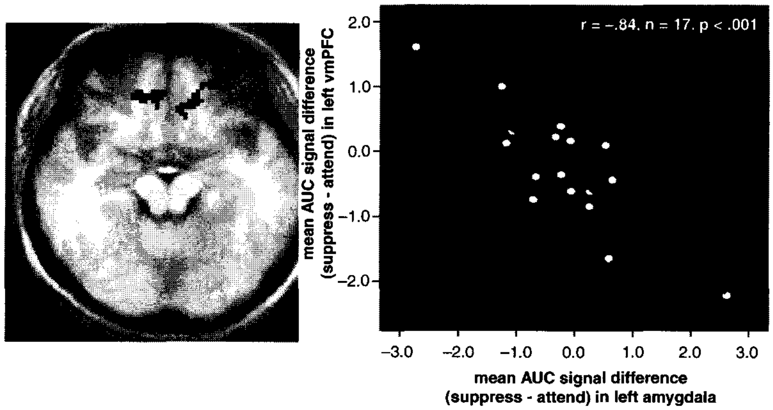

FIGURE 3.2. Increased vmPFC activation that is inversely correlated with activation in the amygdala during the Suppress versus Maintain conditions. Two regions in left and right vmPFC, maximum $t(16) = -4.79$ at Talairach coordinates $x = -23$, $y = 43$, $z = -10$, and maximum $t(16) = -5.28$ at $x = 5$, $y = 37$, $z = -12$, respectively, demonstrate an inverse functional association with the left amygdala. Data from Urry et al. (2006).

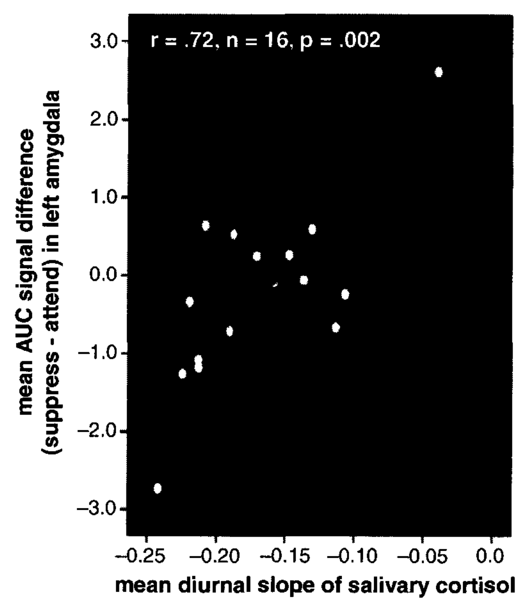

FIGURE 3.3. Relations between MR signal change in the amygdala during Suppress versus Maintain regulation conditions on the ordinate and mean of diurnal cortisol slope calculated within subjects across 7 consecutive days of sampling. Data from Urry et al. (2006).

amygdala in response to the Suppress versus Maintain conditions show the flattest cortisol slope.

The inverse of this effect was obtained for the vmPFC cluster, as the amygdala and vmPFC clusters were themselves highly inversely correlated. Further examination of these effects reveals that it is specifically cortisol levels in the evening that are associated with MR signal change. Thus, poor regulators (i.e., those with less vmPFC and higher levels of amygdala activity during the voluntary downregulation of emotion) are the ones with the highest levels of cortisol in the evening, suggesting that short-term laboratory measures of voluntary regulation are related to longer-term neuroendocrine regulation.

A variety of other data at both the animal and human levels implicates territories in PFC, particularly vmPFC, in the modulation of limbic activity, especially activity in the amygdala during tasks and contexts where regulation can be inferred. For example, Phelps, Delgado, Nearing, and LeDoux (2004) have provided compelling evidence in humans for activation of vmPFC during extinction of conditioned fear, a finding that is consistent with rodent evidence implicating this region in extinction learning and the modulation of amygdala activity (Quirk, Russo, Baron, & LeBron, 2000; Quirk, Likhtik, Pelletier, & Pare, 2003). In addition, Amat et al. (2005) have recently demonstrated the importance of vmPFC in the rodent for the modulation of the dorsal raphe nucleus in response to a stressor.

Evidence suggests that dysfunction in PFC and amygdala are common in depression (see Davidson et al., 2002b for review). Recent data suggest that depressed patients require significantly greater lateral PFC activation than controls to maintain the same level of performance on a working-memory n-back task (Harvey et al., 2005). Other evidence suggests that the polymorphism in the human serotonin transporter gene that has been found to confer susceptibility for affective disorders (Caspi et al., 2003; though see Surtees et al., 2006, for a nonreplication) also is associated with accentuated functional activity in the amygdala (Hariri et al., 2005), and related evidence indicates that this polymorphism may be specifically associated with abnormalities in coupling between vmPFC and amygdala (Heinz et al., 2005). In addition, we have speculated that PFC abnormalities may lead to difficulties in regulating negative affect and may be expressed as increased rumination in depression (see Davidson, Pizzagalli, Nitschke, & Putnam, 2002b; Davidson et al., 2003a). Finally, failure to sustain PFC activity in positive contexts may be associated with anhedonic symptoms and lack of motivation (Pizzagalli, Sherwood, Henriques, & Davidson, 2005).

There are several key outstanding issues that have not been addressed in the extant literature. Of central importance is the issue of individual differences. Little work has focused on the nature and correlates of individual differences in emotion regulation and even less work has addressed possible differences in the neural substrates of emotion regulation in patients with various forms of mood and/or anxiety disorders. A second key issue concerns the correlates of variations in emotion regulation in endocrine and autonomic output though our recent findings described earlier begin to provide a window on this question. We know that the central nucleus of the amygdala provides an important bridge to both autonomic and endocrine outputs, but there has been little study to directly address this issue. A third issue is whether individual differences in basic mechanisms of cognitive control (i.e., the ability to orchestrate thought and action in accordance with internal goals) predict individual differences in emotion regulation. There are no data in the literature that directly bear on this important question, though some theoretical accounts strongly suggest this to be the case (see Barrett, Mugade, & Engle, 2004, for review). Virtually no data are available on relations between short-term measures of regulation in the laboratory and longer-term regulatory processes. Such longer-term regulatory processes may have consequences for peripheral biology that are health-relevant (e.g., Davidson, 2004a). Finally, what few data are available on individual differences in emotion regulation do not rigorously separate the contributions of variations in emotional reactivity from those associated with emotional reactivity. This is a difficult conceptual and methodological problem.

Summary

The existing work points to the importance of prefrontal and amygdalar circuits in the regulation of negative affect and suggests that the functioning of these circuits might be consequential for adapting to adversity. We suggest that prefrontal and amygdalar circuits play an important role in regulating emotion and in modulating vulnerability to psychopathology. This framework, though indirectly supported in the studies described previously, has yet to be tested explicitly. Moreover, while the extant literature on the brain bases of emotion regulation provides important insights into the roles of prefrontal cortex and amygdala, there are limitations to the work to date. For one, there are inconsistencies with regard to the timing of regulation instruction delivery. In some studies, regulation instructions are provided prior to the appearance of the emotion-eliciting stimulus. The consequence is that one cannot verify that the emotion-eliciting stimulus actually provoked an emotion prior to the application of regulatory processes. In addition, some studies are limited to all males or all females or the sample size is too small, and only one study has so far reported on the neural substrates of regulating positive affect. These issues call into question the generalizability of some of the findings. Finally, while the studies in humans have emphasized intrinsic emotion regulatory processes, they have devoted considerably less attention to extrinsic factors that modulate emotion regulation. Here the development of a nonhuman primate model is particularly important. In addition, studies in nonhuman primates provide a powerful opportunity for the examination of individual differences in emotion regulation because animals at the extremes of distributions can be selected for more intensive study.

CONTEXT AND REGULATION IN A NONHUMAN PRIMATE MODEL

The role of context in the regulation of affective reactivity is relatively understudied, particularly at the human level. Numerous studies at the animal level have demonstrated the importance of context in the regulation of affective behavior and have highlighted the role of the hippocampus (Anagnostaras, Maren, & Fanselow, 1999) and interconnected structures (bed nucleus of the stria terminalis: Davis & Lee, 1998) in this type of process. The contextual regulation of emotion is assumed to proceed relatively automatically. The organism apprehends context and based on the output of an analysis of current context, behavior is adjusted in a contextually appropriate manner. To study the role of context in emotion regulation, it is necessary to evaluate aspects of emotional responsivity in two or more contexts so that a comparison across context can be made.

Some forms of psychopathology that involve disorders of affect may be best conceptualized as disorders of the context regulation of affect. For example, both mood and anxiety disorders typically involve the expression of normal emotion in inappropriate contexts. That is, the emotion expressed in these disorders would be normative and appropriate in certain contexts. In the diagnostic criteria for major depression following bereavement, the depression must persist for more than 2 months to be labeled major depression according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994). In other words, the continued expression of depressed affect beyond the context in which it is deemed appropriate is central to the diagnosis. In many of the anxiety disorders, the fear and other emotions that might be experienced are perfectly normal emotions. They are simply expressed at inappropriate times in nonnormative contexts. Thus, the fear that a social phobic might experience in the course of interacting with a group of people is not in itself pathological. What makes the expression of the fear pathological is the fact that it is expressed in contexts in which most other individuals do not experience such fear.

In an effort to investigate context-inappropriate emotion in nonhuman primates, Kalin (Kalin & Shelton, 2000) examined 100 rhesus monkeys in a series of behavioral tests called the Human Intruder Paradigm that have been used extensively in his laboratory (see Kalin & Shelton, 1989). These tests involve exposure of a monkey to three specific conditions. In one condition, the animal is alone; in a second condition, a human enters the room and exposes his profile to the animal (the No Eye Contact condition); in a third condition, the human enters the room and stares at the animal. Each of these conditions is presented for 10 minutes. During each condition, various behaviors of the animal are coded. In previous work, Kalin has demonstrated the differential sensitivity of the different behaviors to specific pharmacological manipulations (Kalin & Shelton, 1989). Normatively, monkeys freeze when exposed to the human profile. Interestingly, there are individual differences in freezing duration and these differences are stable over time (Kalin, Shelton, Rickman, & Davidson, 1998). In response to both the Alone and the Stare conditions, the normative response of monkeys is to display little if any freezing, with other behaviors increasing in frequency during these conditions. When a very large group of animals is tested ($N = 100$), the pattern of normative behavior previously observed is confirmed at the group level. There is a highly significant difference in freezing duration among the conditions such that freezing is significantly higher during the No Eye Contact (NEC) condition compared with the other two conditions. However, there are also marked individual differences, not only in the duration of freezing during the normative condition (No Eye Contact) but also in the duration of freezing during the other conditions. There were three animals in this group of 100 that displayed levels of freezing during the Stare condition that were very high and indistinguishable from their freezing duration during the normative NEC condition (see Figure 3.4). Note that the freezing of this small subgroup of three was high during the No Eye Contact condition, but there were quite a few other animals who displayed levels of freezing that were comparable during this condition. However, all but these three animals turned off this response during the other conditions. These three animals can be said to be displaying context-inappropriate freezing. In analyses of biological data (prefrontal activation asymmetry and cortisol) it was found that these three animals had markedly more extreme patterns than their counterparts who froze for an identical duration of time during the normative context (Kalin & Shelton, 2000).

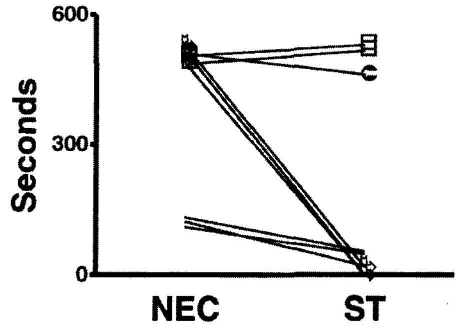

FIGURE 3.4. Freezing duration in seconds (out of a total of 600 seconds) in response to the No Eye Contact (NEC—exposure of the monkey to a profile of a human) and the Stare (ST) conditions in three groups of animals: One group shows very long durations of freezing during the normative context (NEC) but then freezes little during ST. A second group shows virtually no freezing during either NEC or ST. Finally, the third group exhibits high levels of freezing in response to both NEC and ST. This is the group that displays out-of-context freezing (i.e., during ST). The group of three animals who show the out-of-context freezing are the only animals in a group of 100 to exhibit this pattern. From Kalin and Shelton (2000). Copyright 2000 by Oxford University Press. Reprinted by permission.

While a mechanistic understanding of such context-inappropriate affective responding is not yet available, there are several issues that warrant comment. First, given the role of the hippocampus and bed nucleus of the stria terminalis that have been featured in rodent models of context conditioning (Davis & Lee, 1998), it is likely that these brain regions play a role in the context regulation of affective responding in humans. It is noteworthy that in several disorders that are known to involve context-inappropriate affective responding, morphometric study of hippocampal volume with high-resolution MRI has revealed significant atrophy (e.g., Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Sheline, Sanghavi, Mintung, & Gado, 1999; Bremner et al., 1995, 1997). Such atrophy may arise as a consequence of exposure to elevated levels of cortisol, as several authors have hypothesized (Gold, Goodwin, & Chrousos, 1988; McEwen, 1998), though recent twin research has suggested that smaller hippocampal volume may be a predisposing vulnerability factor in the development of at least some of these disorders, in this case posttraumatic stress disorder (Gilbertson et al., 2002). At the human level, age-related declines in hippocampal volume have been related to elevated cortisol levels. The consequences of such age-related changes have been examined in the cognitive domain, specifically measures of declarative memory that are thought to be hippocampally mediated (Lupien et al., 1998). However, there has been no study of which we aware that has specifically related hippocampal morphometric differences to context-dependent affective responding. Based on the issues described previously, it is likely that variations in hippocampal structure and in connectivity between hippocampus and PFC will also be accompanied by profound affective changes and will impair an organism's ability to adaptively regulate emotion in a context-appropriate fashion. The affective consequences of hippocampal dysfunction may be as, if not more, important to the adaptive functioning of the organism as the cognitive changes that have been featured so prominently in the human literature. One of the important challenges in this area for the future is to develop a better understanding of context from a human perspective because most previous studies have been conducted at the nonhuman level (and mostly in the rodent) and have relied on simple manipulations of housing conditions to alter context.

The second issue that deserves emphasis here is the implications of the work on context and its role in shaping affective responding for assessing certain behavioral traits. We use behavioral inhibition as our example here in part because the studies we have conducted in nonhuman primates have been designed to model human behavioral inhibition. In the developmental literature on human infants and toddlers, this temperamental characteristic has typically been assessed by observing behavioral signs of fearfulness and wariness in contexts of novelty and unfamiliarity (e.g., Kagan, Reznick, & Snidman, 1988). Thus, for example, behavioral inhibition (one measure of which is freezing) has been coded when toddlers are approached by unfamiliar strangers or bizarre-looking robots. These are situations in which it is normative to show some wariness. In fact, the display of high levels of approach behavior in this context is the nonnormative, context-inappropriate response. As we noted earlier, there appear to be important differences between monkeys who express identically high levels of freezing during the normative context (exposure to the human profile) but differ in their duration of freezing during a nonnormative context (exposure to the human staring). Were the assessment period with these monkeys restricted to the normative context, the group of high freezing animals would have been classified identically. Only by including an assessment of their behavior in a nonnormative context were behavioral differences revealed, which helped to account for some of the variance in basal levels of prefrontal activation asymmetry and cortisol (Kalin & Shelton, 2000). These findings imply that our assessments of human behavioral inhibition may not be nearly as sensitive as they might. Rather than performing such assessments in the context-appropriate conditions of novelty and unfamiliarity, perhaps we should be measuring these temperamental characteristics in nonnormative contexts. We would hypothesize that individuals who habitually fail to regulate their affective responses in a context-sensitive fashion may have functional impairment of the hippocampus and/or stria terminalis. Such functional impairment may arise as a consequence of plastic changes in these regions as a function of cumulative exposure to elevated glucocorticoids (McEwen, 1998) or they may arise from a genetic predisposition to have compromised hippocampal structure and function (e.g., Gilbertson et al., 2002).

It has been known for some time that neurogenesis (the growth of new neurons), primarily in the dentate region of the hippocampus, can occur in the postnatal period in rodents (see Gould & McEwen, 1993, for review). However, it has only recently been demonstrated that such plastic changes can occur in the adult human hippocampus as well (Eriksson et al., 1998). The fact that such neurogenesis can occur in adult humans raises the possibility that both salubrious as well as stressful conditions might influence this process and that these experience-induced hippocampal changes, in turn, can have significant affective and cognitive consequences. Kempermann, Kuhn, and Gage (1997) have demonstrated that exposure of adult mice to an enriched environment produced a 15% increase in granule cell neurons in the dentate gyrus of the hippocampus compared with littermates housed in standard cages. This basic phenomenon has been recently replicated in rats (Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999) and extended by demonstrating that the rats raised in an enriched environment who showed neurogenesis in the dentate gyrus also demonstrate improved performance in a spatial learning test. Conversely, it has been shown that stress diminishes proliferation of granule cell precursors in the dentate region of adult marmoset monkeys (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). Collectively, these findings highlight the plasticity of certain regions of the brain that persist into adulthood and raise the possibility that interventions, even those occurring during adulthood, not only can have effects on neuronal function but can also literally influence neurogenesis. The fact that the focus of this work is in the hippocampus indicates that a major substrate of context-dependent emotional responding is a key target for these experientially induced changes. It is likely that other brain regions as well will exhibit plastic changes. Whether these will involve neurogenesis or will favor other mechanisms is a question that must be addressed in future work. For now, the extant findings provide a rationale for examining the impact of therapeutic interventions, both pharmacological as well as behavioral, as well as naturally occurring environmental stressors and stress buffers, on neuronal structure and the central circuitry of emotion regulation, that might underlie changes in affective style.

In more recent work on our nonhuman primate model of emotion regulation, we have used microPET with fluorolabeled deoxyglucose (FDG) to label regional glucose metabolism in the monkey brain. This procedure is ideally suited to study whole-brain changes in activation in response to naturalistic challenges in monkeys. In this procedure, animals are exposed to standardized behavioral challenges. In our case here, we used the Human Intruder paradigm described earlier. Animals are injected with FDG prior to exposure to these challenges. FDG is taken up in the brain over the course of an approximately 30-minute period. After this 30-minute period has elapsed, the FDG is trapped in the neurons for a couple of hours before it is metabolized. Thus, the integrated activity over the course of an approximately 30-minute period produced by the behavioral challenge will be reflected in the distribution of FDG in the brain. Following this initial 30-minute period, the animals are then anesthetized and placed in the microPET scanner. The images we obtain reflect the integrated activity from the prior 30-minute period.

Using this method, we (Kalin et al., 2005) recently showed that glucose metabolism in a region that includes the bed nucleus of the stria terminalis (BNST) and the nucleus accumbens is highly correlated with the duration of freezing both in the normative context (i.e., during the NEC condition) as well as in the nonnormative context (in this case, while the animal was alone; see Figure 3.5).

We next addressed the question of which brain regions changed their pattern of activation in different contexts and predicted behavioral changes in the two contexts. To address this question, we examined relations between the change in freezing from the Alone to the NEC condition and changes in glucose metabolism between these two conditions. There were several regions that emerged from this analysis but the most important one was the dorsal anterior cingulate cortex (dACC) region. There was a very strong relation between change in dACC activity and change in freezing such that animals who showed higher durations of freezing during the NEC compared with the Alone conditions showed higher levels of glucose metabolism during NEC compared with Alone in the dACC.

Collectively the findings from this study demonstrate that the BNST region, previously linked to anxiety by Davis and colleagues (Davis & Lee, 1998) is strongly associated with freezing across contexts. However, alterations in metabolic rate in this region was not associated with changes in freezing between contexts. The dACC was very strongly associated with changes in freezing between contexts. This region of dACC (BA 24c) has direct projections to motor cortex (Dum & Strick, 2002) and has been linked to conflict monitoring and error detection when divergent motor responses are

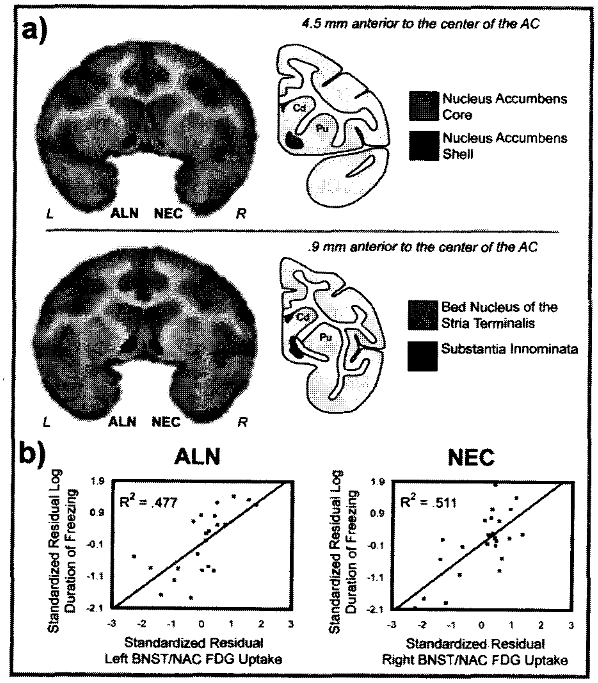

FIGURE 3.5. The BNST/nucleus accumbens (NAC) regions that are correlated with freezing duration in the NEC (red) and Alone (ALN; blue) conditions are displayed. (A) more anterior region of the BNST/NAC; (B) a more posterior region. Scatter plots represent the relation between log freezing duration and brain activity in the BNST/NAC regions of interest for the ALN and NEC conditions. Both variables are standardized and residualized for age. From Kalin et al. (2005). Copyright 2005 by the Society for Biological Psychiatry. Reprinted by permission.

required, as would appear to be the case in shifting between contexts that normatively have very different signatures of motor output.

Another important feature of contextual regulation of emotion in nonhuman primates concerns the manner in which contextual support is used or requested. Regions of the PFC likely play a role guiding behavior in a goal-directed manner to reduce distress and regulate negative affect. This process can be effectively studied in monkeys by using microPET in conjunction with another naturalistic challenge–separation of an infant from its mother. In much earlier research conducted in Davidson's laboratory, Davidson and Fox (1989) separated 10-month-old infants from their mothers for a brief 30-second period and examined the extent to which they cried in response to this challenge. Prior to the separation period, baseline levels of prefrontal activation were assessed with brain electrical measures. They found that infants who cried in response to maternal separation had higher levels of right-sided prefrontal activation during the prior baseline period compared with infants who did not cry. One interpretation of these findings is that right PFC is playing some role in guiding behavior toward the reduction of the negative affect elicited by separation. In this case, the crying can be viewed as a signal to reinstate contact with the mother. On the other hand, if infants were extremely fearful and hypervigilant for threat-related cues in response to this challenge, we might expect that they would be less likely to cry. Crying in this case provides a clear signal to possible predators about one's location.

Based on the aforementioned conjectures, we designed a study in monkeys to test some of the hypotheses to have emerged from a consideration of the human data (Fox et al., 2005). Our experiment was based on earlier observations from the Kalin lab (Kalin & Shelton, 1989) indicating that in response to separation, the normative response of monkeys is to coo, though there are large individual differences in the duration of cooing displayed. To explain the variation across individuals, we hypothesized that animals who perceived this challenge as a threat and thus would strongly activate the amygdala would show less cooing while those animals who directed their behavior toward reinstating contact with the mother and thus cooing more would show increased activation in the right dorsolaeratal PFC. In this experiment, we adopted the same strategy that we used in the other microPET studies with monkeys. In this case, we injected FDG prior to period of separation and then anesthetized the animals and scanned their brain after a 30-minute separation period. We specifically hypothesized that we would find a positive correlation between metabolic rate in the right dorsolateral PFC (dLPFC) and cooing and a negative correlation between metabolic rate in the amygdala and cooing. Figure 3.6a presents the data for the right dlPFC and amygdala.

As can be seen from this figure, animals with higher levels of glucose metabolism in the amygdala show decreased cooing in response to separation while those with higher levels of activation in the right dlPFC show higher levels of cooing. Interestingly, these two neural systems are relatively orthogonal in response to this challenge because when they are added in separate steps of a higherarchical regression, they explain 76% of the variance in cooing behavior (see Figure 3.6b).

In a very recent study we used the Human Intruder paradigm to select extreme groups of monkeys based on the duration of freezing they exhibited in response to the NEC challenge. We hypothesized that animals with the highest levels of freezing, akin to human behavioral inhibition, would show the highest levels of amygdala activity. In addition, we further predicted that in response to separation, the most behaviorally inhibited animals would show the least amount of cooing. Figure 3.7 presents the data on freezing behavior in three groups of animals that we tested further. Figure 3.8 shows the PET data and illustrates that the high-freezer group exhibits the highest levels of glucose metabolism in the amygdala compared with the other two groups. For reasons we do not yet understand, the middle group actually showed the lowest levels of amygdala activation compared with the high and the low group freezer groups. Figure 3.9 presents the data in a continuous fashion across groups and reveals that animals with the highest levels of amygdala activation (who have the highest levels of freezing in the nonnormative context of being alone) show the least amount of cooing. These findings indicate that the group of animals with the most nonnormative affective expression, in this case high levels of freezing during the Alone condition, were the least effective in calling for help during the Alone condition.

SUMMARY AND CONCLUSIONS

This chapter has selectively reviewed recent empirical studies of the neural bases of emotion regulation in humans and nonhuman primates. The human studies have

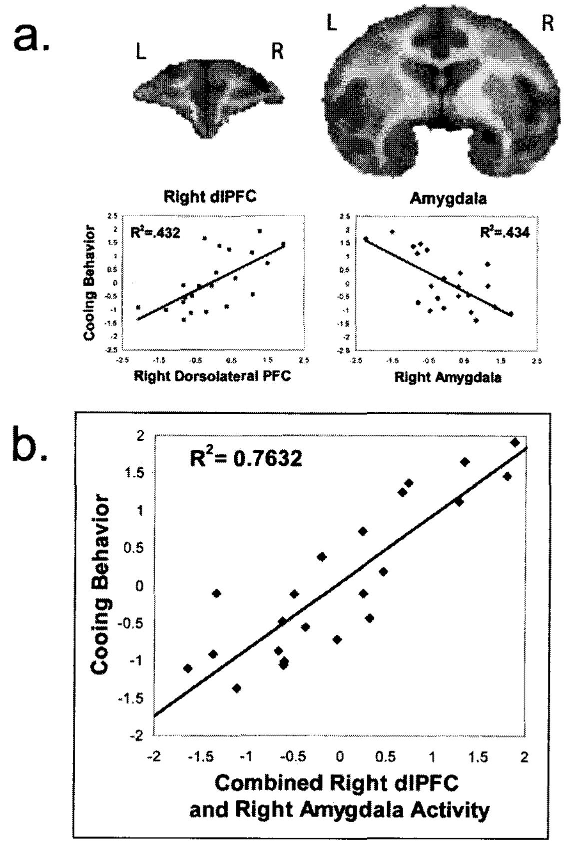

FIGURE 3.6. Relations between glucose metabolic activity in the right dorsolateral PFC and the amygdala and duration of cooing during separation. From Fox et al. (2005). Copyright 2005 by Proceedings of the National Academy of Sciences. Reprinted by permission.

emphasized voluntary emotion regulation, a competence that appears to be if not uniquely human, certainly much more well developed in humans than other species. It was shown that individual differences in the neural correlates of voluntary emotion regulation are related to endogenous regulatory processes in everyday life. We specifically presented new evidence to indicate that those individuals who were poor emotion regulators as reflected in less vmPFC activation and more amygdala activation when attempting to voluntarily downregulate negative affect using cognitive strategies show a flatter slope of the cortisol rhythm. This flatter slope was found to be primarily a function of higher evening levels of cortisol. These findings suggest that laboratory probes of the neural correlates of emotion regulation reflect longer-term regulatory processes that may have important consequences for mental and physical health and illness.

The studies in nonhuman primates highlight the utility and power of studying emotion regulation at this level. There are certain questions primarily related to extrinsic influences on emotion regulation that are very well suited for addressing at the nonhuman primate level, particularly the role of context in shaping automatic emotion regula-

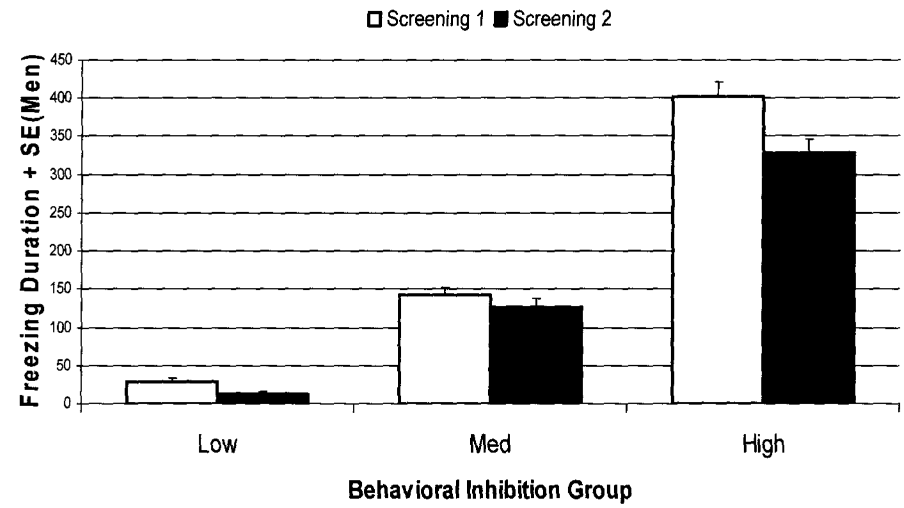

FIGURE 3.7. Durations of freezing at first assessment and follow-up in three groups of animals selected to show extremely high, low, or middle durations of freezing in response to the NEC condition in the Human Intruder paradigm.

tion as well as the recruitment of conspecifics to facilitate emotion regulation. We provided evidence to show that there are important individual differences in the extent to which context regulates emotion. The failure to regulate emotion in a context-appropriate fashion may reflect unique neurobiological processes. We believe these findings have important implications for human studies that assess emotion reactivity in normative contexts. Furthermore, there is a critical need to develop novel paradigms in humans that address the contextual regulation of emotion and that characterize individual differences in such processes. We believe that individual differences in the

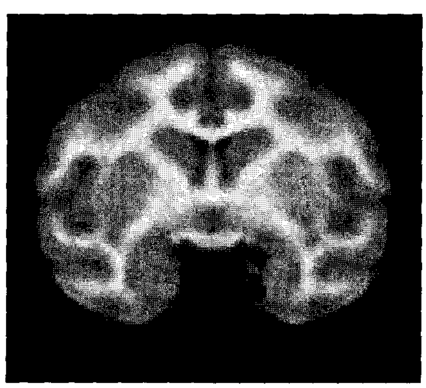

FIGURE 3.8. Region of the amygdala where the high-freezer group shows significantly greater amygdala metabolism compared with the other two groups in response to the Alone condition.

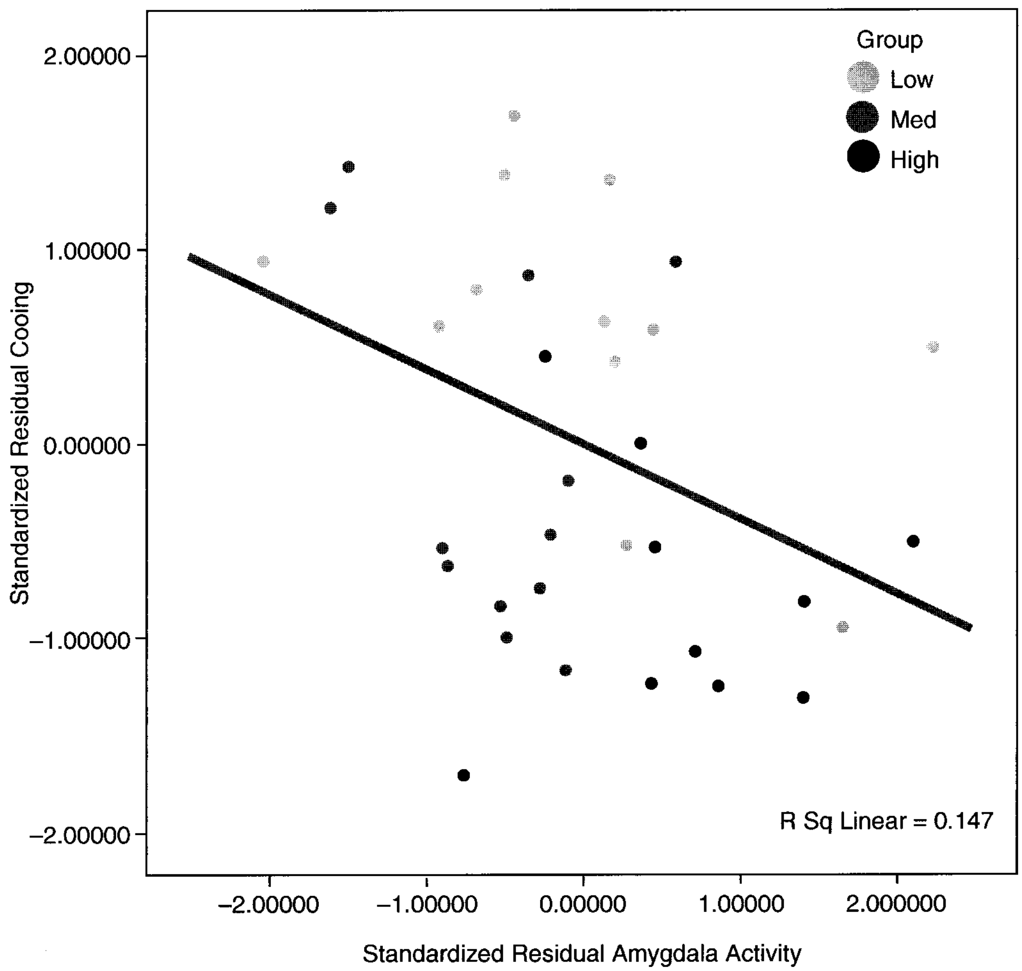

FIGURE 3.9. Relation between glucose metabolism in the amygdala and cooing. Animals who show the highest level of glucose metabolism in the amygdala coo the least.

context-dependent automatic regulation are crucially important in governing vulnerability to psychopathology; assessment procedures that capture such individual differences in humans require development. In animals whose environments are highly controlled, it is easier to manipulate context compared with the human case where the very term "context" is difficult to operationalize. Our capacity for top-down control, to voluntarily cast our attentional spotlight selectively to certain features of our environment enables context to be changed through the endogenous regulation of attention. This is clearly an area in which additional research is required and in which creative new strategies inspired by the nonhuman work are needed.

It is clear that advances in the understanding of the neural bases of emotion regulation will be greatly facilitated by combining the insights derived from both human and nonhuman studies and that both approaches are necessary to fully characterize the complexities of emotion regulation and dysregulation.

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