Characterizing the functional architecture of affect regulation:

Emerging answers and outstanding questions

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Marcus Aurelius was a thinking person's Roman Emperor, and his *Meditations* has been counted among the most introspective of ancient philosophical works. Among the many observations about society, leadership, life, and death that fill this diary-like text is one whose importance might be overlooked by the casual reader. Aurelius meditated that, "If you are distressed by anything external, the pain is not due to the thing itself, but to your estimate of it; and this you have the power to revoke at any moment." A careful reader might catch the twofold impact of these words, however. First, they convey the insight that the world is what we make of it, and that our mental machinery constructs our experience of the world. Second, they betray Aurelius's role as Rome's Commander in Chief, who knew full well the specific power of pain, and of negative affect more generally, to cripple even the heartiest of soldiers. Aurelius sought to understand how one might be protected from the consequences of injury - both psychic and physical.

A full appreciation of Aurelius's insights may have never been more timely. Our modern landscape may lack Roman emperors and Roman legions, but it is full of everyday battles both personal and societal. We pursue professional success. We wrestle with romantic relationships. We confront conflicted feelings. We intervene in intergroup conflicts. We wage war on terrorism. Over two millennia ago a Philosophic General echoed sentiments shared by philosophers before him, and presaged the message of countless scholars and psychologists ever since: The mind is a double-edged sword. Swung one way, it serves your enemy, causing distress and pain. Swung another, it serves your champion, cutting a swath through fear, through grief, through false belief. Indeed, your mind is the best weapon you can carry into any battle, for with it you can conquer that most pernicious and inescapable enemy: your own self, and your painful estimate of the world.

How is it that the way we think about and interpret the world determines the way in which we respond to it? How does thinking control negative feeling? Modern multidisciplinary research can provide answers to these questions that move beyond philosophic musings (J.T. Cacioppo, Berntson, Taylor, & Schacter, 2002; Ochsner & Lieberman, 2001). Using the tools of modern neuroscience in combination with the methodology of social psychology, researchers have begun constructing theories that link the experience of negative affect to a set of psychological processes implemented by neural systems that together comprise a functional architecture for affect regulation. This three part chapter considers just how far these explanations have come towards explaining what enables us to adaptively respond to even the most trying of times or pressing of pains. The first part briefly considers what we mean by, "negative affect," and its brain basis, if a negative affective response is what is to be regulated. The second part reviews recent neuroimaging research on affect regulation. The third concludes by summarizing a set of emerging answers to the question of mechanism implied by the preceding review, and highlights outstanding questions that remain to be addressed by future research.

Brain Bases of Affective Evaluation

Emotion and Affect

Although the terms emotion and affect often are used interchangeably by psychologists to refer to valenced feeling states that may be accompanied by changes in physiology and behavior, a useful distinction between the two can be made. Emotion refers to a coordinated set of behavioral, physiologic and experiential responses that ready an organism to adapt to specific environmental challenges (John T. Cacioppo & Berntson, 1999; Feldman Barrett, Ochsner, & Gross, in press; Lazarus, 1991). Emotions are episodic in the sense that they have an eliciting

stimulus or set of eliciting conditions that trigger a response whose trajectory can be described and demarcated by an endpoint. Although debates have raged over the existence of a more or less finite set of basic emotion types, there is consensus concerning a core set of appraisal patterns that determine which emotions are generated as a function of the relationship between external events and internal goals, wants, and needs (Scherer, Schorr, & Johnstone, 2001). By contrast, affect often is considered to be an umbrella term that encompasses not just emotional responses, but enduring moods that lack specific eliciting conditions and consciously perceived referents, as well as moment to moment valenced (i.e. good/bad, or affective) evaluations of external stimuli or internal mental contents.

A full consideration of the merits of differentially inclusive definitional boundaries is beyond the scope of the present chapter (for discussion see (Feldman Barrett et al., in press; Scherer et al., 2001). For present purposes, the term affect will be used for two reasons. The first is that it can usefully refer to various types of phenomena that involve the use of thinking to regulate a valenced response. As considered below, thinking or cognition can be used to regulate one's positive or negative perception of another person or attitude object more generally, as well as to regulate one's own personal experience of emotion. The second is that neuroscience research is increasingly suggesting that a common set of brain systems supports the evaluative processing that colors both person perception and personal experience (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Anderson & Phelps, 2001; W.A. Cunningham, Johnson, Gatenby, Gore, & Banaji, 2003; Ochsner, Feldman, & Barrett, 2001; Elizabeth A. Phelps et al., 1998).

The present chapter therefore will use the term affect regulation to refer either to cognitive control of the judgments and interpretations that lead an individual to perceive another

person in a favorable, prejudicial, suspicious, or friendly light, or to the cognitive control of situation-based appraisals that lead an individual to feel happy, sad, angry, or glad. In keeping with Aurelius's recognition of the pernicious consequences of psychological distress, in recognition of the maladaptive mental and physical consequences of failures to regulate negative emotion (Davidson, Putnam, & Larson, 2000; J. J. Gross, 1998b), and in light of the fact that much more is known about the neural bases of negative than positive affect, the focus here is on regulating negative affective evaluations.

Affective Evaluation and the Amygdala

In the past decade, evidence from both human and animal research has implicated the amygdala, an almond-shaped subcortical set of nuclei near the tip of the temporal lobe's medial wall, in a number of functions intimately related to affective evaluation. Studies of fear conditioning in rats, for example, initially demonstrated that the amygdala was critical for associating neutral unconditioned stimuli with aversive conditioned stimuli such as electric shocks (LeDoux, 2000). These findings have been confirmed by subsequent studies of human patients with amygdala damage (LaBar, LeDoux, Spencer, & Phelps, 1995) who fail to show autonomic evidence of fear conditioning, as well as imaging studies of healthy participants who show amygdala activation during the acquisition and expression of conditioned fear (Buchel & Dolan, 2000).

The amygdala seems to play a special role in the automatic, rapid, early, and even preattentive detection of affectively relevant stimuli. This hypothesis was initially based on the discovery that a subcortical pathway from sensory organs to amygdala, which bypassed the cortex, was sufficient to support conditioned fear in rats (LeDoux, 2000). This suggestive finding was not directly tested, however, until functional imaging studies demonstrated

amygdala activation to subliminal presentations of fear faces (Whalen et al., 1998) and during the conditioning of responses to subliminal fear faces cues (Morris, Ohman, & Dolan, 1999). More recent studies have shown that the amygdala's response to subliminal fear faces is exaggerated in depression, but normalizes after successful treatment (Sheline et al., 2001), and that amygdala lesions may block the attention grabbing power of briefly presented affectively charged words (Anderson and Phelps, 2001).

In addition to its role in the acquisition of stimulus-response associations, the amygdala is important for consolidating explicit memory for emotionally arousing events. Building on a large rodent literature linking the amygdala to arousal-mediated learning, Cahill and colleagues found with a human sample that drugs blocking norepinephrine release in the amygdala eliminated the memory enhancement typically found for the emotional components of a story (Cahill, Babinsky, Markowitsch, & McGaugh, 1995). Subsequent imaging studies have linked amygdala activation during the encoding of both positively and negatively arousing photographs to subsequent memory for them (Hamann, Ely, Grafton, & Kilts, 1999).

More broadly, amygdala activation has been observed in response to a wide variety of stimuli with intrinsic or learned affective significance, including pleasant and unpleasant odors (Zald & Pardo, 2000), foods (Zald, Lee, Fluegel, & Pardo, 1998), positive or negative photographs (Hamann et al., 1999) (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003), film clips (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997), and arousing musical passages (Blood & Zatorre, 2001). Amygdala lesions may skew perception of aversive or threatening stimuli in a positive direction, leading to recognition impairments of fear faces, a tendency to perceive as friendly people normatively appearing to be unfriendly, and a tendency to classify normatively unpleasant images as more pleasant (Adolphs, Tranel, & Damasio, 1998). As these

data indicate, the amygdala may play a special role in perceiving social stimuli, a role further supported by the finding that amygdala lesions impair perception of subtle expressions of social emotions (such as interest, boredom, or flirtation; (Adolphs, Baron-Cohen, & Tranel, 2002)) and that greater amygdala activation is found to outgroup than to ingroup members (E. A. Phelps et al., 2000). Indeed, for Caucasian participants, amygdala activation to African-American faces is correlated with the amount of anti-black bias shown on an implicit measure of racial attitudes (reference). Heightened amygdala activation also may predict psychiatric outcomes, including the presence or severity of depression (Abercrombie et al., 1998), and accompanies evoked symptoms of anxiety, phobia, and excessive compulsive disorder (Phillips, Drevets, Rauch, & Lane, 2003).

Beyond the amygdala, a number of other richly interconnected brain structures play an important role in affective evaluation. The first is the ventral striatum, which is intimately linked to the experience and prediction of rewards (Knutson, Fong, Adams, Varner, & Hommer, 2001). The second is the midportion of the cingulate cortex, which plays a special role in representing the unpleasant properties of physical pain, and may more generally serve to signal a morning the current behavior is not meeting desired ends (Ochsner et al., 2001) (Peyron, Laurent, & Garcia-Larrea, 2000). The third is the insula, which like the cingulate is responsive to physical pain, also signals the presence of disgust-related stimuli (Peyron et al., 2000). The fourth, and for present purposes, last, is the orbitofrontal/ventromedial prefrontal cortex (PFC; which includes ventral lateral PFC as well), which is sensitive to many of the same classes of stimuli processed by the amygdala, but seems to play a special role in altering existing affective associations. Thus, orbitofrontal lesions in primates (Dias, Robbins, & Roberts, 1997) and in humans (Fellows & Farah, 2003) impair the ability to alter a stimulus-reinforcer association once it is learned, and

single unit recording studies in rats and primates suggest that orbitofrontal cortex neurons change their firing properties to previously rewarded (but now not rewarded) stimuli more rapidly than do amygdala neurons (Rolls, Critchley, Mason, & Wakeman, 1996). If the amygdala provides an initial appraisal of the affective relevance and potential threat value of stimulus, the ventral striatum, anterior cingulate and insula may code additional affective properties relevant to specific types of stimuli, and the orbitofrontal cortex constructs a higher-level representation that places the affective value of a stimulus in its current goal-relevant context (M. D. Lieberman, 2000); (Ochsner & Feldman Barrett, 2001; K. N. Ochsner & J. J. Gross, 2004).

On balance, the available literature implicates the amygdala more than any other brain structure in affective evaluation, and especially in the generation of a negative evaluation that may bias the perception of social targets and be a first step in the generation of a negative affective experience (Ochsner & Feldman Barrett, 2001). In the following section we review a number of functional neuroimaging studies examining ways in which cognition can be used to modulate evaluation, affect, and the amygdala's response.

The Cognitive Regulation of Affective Evaluation

The use of thinking to control feeling, of cognition to regulate affect, for centuries has been a topic of central concern for philosophers, writers, and psychologists. Indeed, many classic stories involve the struggle to resist temptation, to control an impulse, to understand the nature of one's despair or desire, and thereby be free from its grasp. Whether it's Biblical tales of the very First Family and their inhibitory failures, a Roman Emperor's meditations on the epistemology of pain, the legend of Siddhartha and his Buddhist renunciation of worldly wealth, stories of concentration camp survival, or gossip about the indiscretions of contemporary politicians, humans are always seeking information and telling stories about the way in which

affect can and cannot be brought under the control of reason.

But which stories are correct? Which theories of the way in which cognitive control can impact emotion are correct, and what mechanisms are involved? One approach to answering these questions is to use multiple types of evidence to constrain theories, but until recently information about the brain bases of affect and cognitive control were not brought to bear on these issues. The relative recency of neuroscience approaches to understanding affect regulation in humans, in comparison to long-standing interest in the issue, can be attributed to variety of reasons primarily having to do with availability of brain imaging technology and the establishment of a firm foundation of neuroscientific knowledge concerning the brain bases of simple behaviors; for discussion see (Ochsner, 2004; Ochsner & Lieberman, 2001).

A simple framework can be used to organize understanding of data from different domains of neuroscience research relevant to questions about affect regulation. Cognitive processes can be seen as impacting emotion generation processes at three different stages: the first involves the initial attention to, and gating of, stimulus inputs for further processing; the second involves the use of thinking to re-interpret or manipulate the meaning of an input once it has been gated into the system; and the third involves the inhibition, selection or modulation of expressive behavioral responses (J. J. Gross, 1998b; K. N. Ochsner & J. J. Gross, 2004).

Building on the findings from studies of ‘cold’ forms of cognitive control, a working hypothesis has developed concerning the cognitive control of affect. The basic idea is that at whatever stage they might intervene, control processes used to regulate are supported by frontal and cingulate systems (Miller & Cohen, 2001) that may modulate affect generation systems such as the amygdala, insula, and pain-related cingulate cortex; which specific systems are involved may depend upon the specific type of emotion and the specific kind of regulatory strategy

employed (Kevin N. Ochsner & James J. Gross, 2004; Ochsner et al., 2004) the control processes used to regulate depend upon frontal and cingulate systems that implement cognitive control processes. Prefrontal cortex is thought to be involved in retrieving information from semantic memory, holding information in mind, and maintaining representations of strategic (e.g. regulatory) goals (Miller & Cohen, 2001), and anterior cingulate cortex is thought to monitor the extent to which ongoing control is achieving its desired ends, signaling the extent to which desired and states have not yet been met (Matthew D. Lieberman, Gaunt, Gilbert, & Trope, 2002; Miller & Cohen, 2001; K. N. Ochsner & J. J. Gross, 2004). As will be seen, available data generally supports this hypothesis, with one important caveat: the vast majority of extant studies have investigated only the regulatory dynamics involved in the first two stages of affect processing - attentional gating and mental manipulation of meaning, which are of the focus of the following review – whereas none have directly addressed the regulation of affective behavioral responses *per se*.

Attentional Gating

The use of attention to gate sensory input long has been studied in the context of visual object recognition and vision more generally. Neuroimaging studies have examined the extent to which different stages of visual processing are modulated by attention. To the extent that a brain region's activation does not vary as a function of the allocation of attentional resources, the computations carried out by that region may be characterized as taking place "automatically" (or at least with reduced need for conscious, on-line, attentional monitoring). Thus far, for simple non-affective visual stimuli findings have indicated that attention may modulate systems that lie at multiple stages along the visual processing stream, including early systems (such as V1) that represent simple geometric spatial properties of the visual world (Culham, Cavanagh, &

Kanwisher, 2001). In the context of effectively charged stimuli, the question becomes whether systems such as the amygdala or pain-related cingulate cortex, which presumably extract and encode the affective relevance as opposed to visual spatial properties of a stimulus, also are modulated by attention.

Inattention to socioemotional stimuli Five studies have investigated amygdala activation in response to affectively charged as compared to neutral faces during conditions of either full or diminished attention to the face stimuli. Two studies have found that the amygdala's response to of their faces does not vary as a function of attentional resource deployment (Vuilleumier, Armony, Driver, & Dolan, 2001). Vuilleumier and colleagues asked participants make judgments about a display of four stimuli. Two of the stimuli were faces - either neutral or fearful - and two of the stimuli were pictures of houses. Face and house stimuli symmetrically flanked fixation, with the pair of faces or houses either above and below or to the left and right of fixation. On each trial participants were cued to judge whether the horizontal or vertical pair of stimuli were the same or different. This allows comparison of activation to attended (cued direction) and unattended (non-cued direction) fearful faces. Vuilleumier et al. found that fearful stimuli produced greater bilateral activation of the amygdala regardless of the level of attention. By contrast, when viewing faces, activation of the fusiform face area-a cortical region putatively specialized for processing face stimuli-did vary as a function of attention, as did activation of the parahippocampal place area - a cortical region specialized for processing spatial locations - when viewing houses. Similar findings were obtained by Anderson and colleagues who also presented participants with faces and houses under conditions of full and divided attention (Anderson et al., 2003). Their paradigm presented faces and houses semi-transparently displayed on top of one another. Each type of grayscale stimulus was tinted slightly red or green

facilitating attentional selection of the face superimposed on the house (or vice versa). Participants were cued to judge either the gender of the face or a feature of the house on each trial. As was the case for Vuilleumier et al., amygdala responses to fear faces were greater than to neutral faces, and the magnitude of this activation advantage was equivalent when participants attended to and judged face stimuli as compared to attending to and judging house stimuli. Interestingly, insula responses to disgust faces did diminish as attentional allocation to them diminished, whereas the amygdala's response to disgust faces actually increased as attentional allocation to them diminished. This finding suggests that the tuning curve of the amygdala actually broadens when fewer attentional resources are available to identify and discriminate affectively relevant stimuli - when you're distracted, and paying attention to something else, the amygdala responds both to fearful and disgust faces. It remains to be seen just how broad the amygdala's response profile becomes in such circumstances.

In direct contrast to these findings, two other studies have observed amygdala modulation in response to manipulations of attentional allocation. Pessoa and colleagues presented participants with fearful, happy, and neutral faces in the center of the screen and had them perform the task either with full attention, or when performing a concurrent line orientation identification task (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). For the orientation task, vertical or horizontal lines were presented above the face, one on the left and one on the right, and participants judged whether their orientation was the same or different. When performing the orientation judgment, and paying less attention to the faces, amygdala activation to both happy and fearful faces dropped significantly and was indistinguishable from the response to neutral faces. Similar results were obtained by Philips and colleagues using a very different paradigm (Phillips et al., 2004). These investigators presented disgust, fearful and neutral faces

using either 30 millisecond subliminal presentations or 170 millisecond supraliminal presentations. All face presentations were backward masked with a consciously perceived neutral face of the same gender, which participants were instructed to passively view. During supraliminal presentations, fear faces activated the right amygdala and disgust faces activated the insula bilaterally, but both of these activations disappeared during subliminal presentations, suggesting that awareness of the presentation of affectively charged stimuli is necessary for the affective salience of the stimulus to be processed by the amygdala. Strikingly, these findings stand in stark contrast to those of Whalen et al. (1998), who found amygdala activation to subliminal presentations of fear faces. Philips et al. suggest that the discrepancy may have to do with imperfect subliminal presentations by Whalen et al., and possible leakage of affectively charged stimuli into awareness, which was very unlikely in their paradigm because they used rigorous psychophysical testing to establish precise detection thresholds for each participant to make sure that recognition of facial expression on subliminal trials was at chance. A problem for this account, however, is presented by the findings of Cunningham et al., who found greater amygdala activation to black than to white faces in white participants when faces were presented subliminally, but that this difference disappeared when faces were presented supraliminally (W.A. Cunningham et al., in press). Although Cunningham et al. did not verify unawareness of subliminal stimulus presentations as rigorously as did Philips et al., which on Philips' account could explain amygdala activation to subliminally presented black faces, Philips et al.'s account cannot explain *a failure* to find activation to supraliminal presentations of black faces. One possibility is that participants were motivated to actively regulate their responses to black faces when they could consciously perceive them (so as not to have a prejudicial response), and that there is little motivation to regulate responses to consciously perceived fearful faces, which in

experimental contexts may only weakly signal the presence of actual threats. Consistent with this notion, Cunningham et al. found right prefrontal and anterior cingulate activation during supraliminal presentations. Although cingulate activation predicted amygdala deactivation, suggesting conscious regulation of amygdala responding, the regulatory strategy that might have been employed to produce such modulation is unclear.

Beyond the possible use of active regulation, there may be another important factor determining whether or not amygdala modulation as a function of attention to fear-relevant stimuli is observed. To the extent that low-level visual features simply aren't being encoded as one simply fails to attend to and *perceive* those features, is not likely that the information necessary to discriminate affectively-relevant information would be available to the amygdala. Anderson et al. (2003) suggested just this sort of explanation for the findings of Pessoa et al. (2002), and it may be applicable to the findings of Philips et al. (2004) as well. On this account, performing a spatial orientation discrimination task that strongly depends upon parietal systems, or simply failing to register the presentation of fear faces, would deprive temporal lobe systems that extract facial features of the information they need to pass along to the amygdala so that it may signal the presence of affectively charged fearful or disgusting face.

Distraction during pain A second context in which attentional manipulations have been used to examine the regulation of affective responding is the experience of physical pain induced either by a heated thermode placed on the forearm or a painfully cold compress placed on a body part such as the foot. Rather than manipulating spatial attention, participants are asked to do two things at once: while experiencing painful stimulation, an attention demanding cognitive control task is performed that limits the extent to which participants can attend to the pain. Typically, report of pain affect drops when participants are distracted, and the question is whether

activation in pain-related processing regions drops as well. Frankenstein et al. (2001) were the first to observe exactly this phenomenon. Participants experienced either a nonpainful cool or a painfully cold compress on their foot under conditions of full attention or when asked to silently generate proper names were the names of objects from specific categories. When distracted by the verbal fluency task, reports of pain affect dropped, as did activation of regions of the mid cingulate gyrus. By contrast, during distraction, activation of anterior cingulate regions associated with monitoring, as well as the left dorsolateral PFC, was observed, although it is not clear whether these regions were involved in the active regulation of pain or simply involved in supporting performance of the verbal fluency task.

A subsequent study addressed this question by directly testing for an interaction between pain-processing and cognitive control regions. Bantick et al. asked participants to experience either warm or painful heat while completing either blocks of neutral or interference Stroop trials (Bantick et al., 2002). Pain affect dropped during interference as compared to neutral trials, and an activation interaction was observed between the presence of painful stimulation and the presence of cognitive distraction induced by the Stroop. Two regions associated with cognitive control and awareness of affect - right orbitofrontal cortex and rostral anterior cingulate cortex - were more active when resolving interference in the presence of pain than when resolving interference in the absence of pain, suggesting that they play a role in regulating and responses. A number of regions associated with the experience of pain - including the bilateral insula, thalamus, and mid cingulate gyrus - showed a negative interaction, and were more active during pain in the absence of cognitive interference than during pain in the presence of cognitive interference, suggesting that they were down regulated by distraction.

An important question is the level or stage of pain processing (or affective processing

more generally) that can be modulated by cognitive control. Bantick et al. (2002) demonstrated that distraction can modulate thalamic responses, and Tracey et al. extended these findings by showing that asking participants to, "think of something else," during the experience of thermal pain could modulate activation in a brainstem region known as the periacqueductal gray (PAG) known to be important for descending modulation pain inputs from the spinal cord (Tracey et al., 2002). Although Tracey et al. focus only on PAG activation, and so could not speak to the issue of which regions might have been involved in sending cortically based top-down regulatory instructions, Valet et al. did observe PAG-prefrontal interactions that speak to this issue (Valet et al., 2004). Valet et al. employed a task essentially similar to that employed by Bantick et al., and like Bantick observed that rostral medial prefrontal regions were more active during cognitive distraction in the presence of pain than during cognitive distraction in the absence of pain. Although they did not observe Bantick's negative interaction with pain related processing systems, they did find that activation of pain-related thalamic nuclei as well as the PAG inversely correlated with activation of the rostral medial regions differentially involved in resolving cognitive interference in the presence of pain.

Manipulation of Meaning

In contrast to the attentional gating studies which examine the indirect effects on affective evaluation either of performing a secondary task or of diverting spatial attention, two other types of functional imaging studies have asked participants to actively change their construal of the meaning of affectively charged stimuli. The first type ask participants to engage in cognitive reappraisal, or reinterpretation, of the meaning of photographs or films that elicit various types of negative emotion, so as to increase, maintain, or decrease their negative emotional response. The second type ask participants to selectively evaluate a specified

semantic or perceptual stimulus dimension, such as judging the gender as compared to the emotional expression of a face. Despite their differences, findings generated by these two types of studies have shown similar patterns of PFC-amygdala interactions, as discussed below.

Reappraisal The term reappraisal was first used by the psychologist Richard Lazarus to describe our ability to alter of the trajectory of an ongoing emotional response by changing the way in which one appraises its significance or relevance to current goals, wants, or needs (Lazarus, 1991). In an early study, he demonstrated that providing a stress-reducing appraisal frame for emotional the arousing and distressing film about a penile circumcision ritual (it's not that painful; those undergoing the ritual are honored to undergo it, etc.) showed diminished physiological activation relative to participants who did not receive this frame (Lazarus & Alfert, 1964). Although subsequent studies examined the consequences of, and context for, reappraisal (see Gross, 1998 for review), until recently no studies have attempted to unpack the psychological and neural dynamics underlying reappraisal. One of the first studies to do so asked participants to view aversive photographs in one of two conditions: in a baseline condition participants were instructed to simply attend to and be aware of their emotional responses, but not to try and change them, and in a reappraisal condition, participants were instructed to reinterpret the meaning of each photo so as to lessen its emotional punch (Ochsner, Bunge, Gross, & Gabrieli, 2002). For example, participants could reappraise an otherwise sad photograph of four women crying outside of a church as involving a wedding rather than a funeral, which would be an occasion for tears of joy rather than sadness. Right amygdala activation to aversive photographs dropped significantly during reappraisal, as did subjective reports of negative affect, whereas regions of left dorsal and inferior PFC as well as anterior cingulate became active when reappraising. Importantly, activation of left inferior PFC

predicted amygdala deactivation, directly implicating these regions as the mechanistic substrate of reappraisal.

Compatible findings were obtained by Beauregard et al. who asked male participants to inhibit their emotional responses to sexually explicit and arousing film clips by becoming a detached observer (Beauregard, Levesque, & Bourgouin, 2001). Right amygdala and hypothalamic activation found for the arousing film was absent during attempted inhibition, and right dorsolateral prefrontal and anterior cingulate activation was found during inhibition but not during arousal. One problem with this study, however, is that the condition in which participants inhibited their emotional responses while watching sexually arousing film clips always occurred after the condition which participants simply watched arousing clips and let themselves respond in an unregulated fashion. This means that diminished activation of affect-related structures could be due either to habituation to the arousing film clips, to active regulation, or both, and with the present design it is impossible to discriminate among these possibilities. Beauregard and colleagues (Levesque et al., 2003) used a similar distancing instruction to investigate the reappraisal of sad films that were presented in counterbalanced order with baseline unregulated viewing. Consistent with their prior findings, they found that distancing activated regions of right dorsal lateral as well as lateral orbital frontal cortex, and compared to baseline, deactivated the left amygdala, insula, and right ventral PFC.

The use of thinking to regulate feeling is done not only in the service of decreasing feelings, but the service of increasing them as well. Indeed, when we worry, make ourselves anxious, and ruminate about disappointments and losses - whether real or imagined – we de facto up-regulate, or at least maintain, our negative emotion that might otherwise have diminished or dissipated. Ochsner and colleagues compared the use of reappraisal to increase and decrease

negative emotion to determine whether these two uses of reappraisal depend upon similar or different control systems, and whether they might modulate similar affect processing systems, albeit in different ways (Ochsner et al., 2004). They found that cognitively increasing or decreasing negative emotion recruited left lateral prefrontal and anterior cingulate cortex, that increasing selectively depended upon left dorsal medial prefrontal systems involved in the metacognitive generation of negative information (Cato et al., 2004), that decreasing selectively depended upon right lateral and orbital frontal systems involved in response inhibition (Garavan, Ross, & Stein, 1999), and that the right amygdala was modulated up or down in accordance with the goal of reappraisal. These findings substantially replicated those of Ochsner et al. (2002), although the earlier study did not find right lateral prefrontal activation when decreasing, a finding Ochsner et al. (2004) noted was present in the earlier study at a lower threshold and may have been detected in the later study because of greater power (which included a more sensitive pulse sequence combined with greater N). Sheaffer et al. found consistent results by observing bilateral maintenance of amygdala activation after viewing aversive photographs when participants used reappraisal to maintain their negative feeling (Schaefer et al., 2002). This study did not constrain strategies, or report regions of prefrontal activation, so it is difficult to determine which regulatory mechanisms are responsible for these effects.

Selective evaluation Studies manipulating the stimulus dimension specified for construal all contrast a condition in which participants explicitly evaluate the affective valence of a stimulus or their response to it with a condition asking participants to judge some property that is not explicitly affective and/or could be inferred straightforwardly from perceptual features.

One of the first studies to examine construal in this way came from Hariri et al. who used a matching task in which participants judged which of two comparison stimuli presented at the

bottom of the screen matched a target stimulus presented at the top of the screen (Hariri, Bookheimer, & Mazziotta, 2000). In the perceptual condition, all three stimuli were faces that expressed anger or fear. In the labeling condition only the target stimulus was a face and comparison stimuli were expression labels (i.e. the words angry or afraid). Greater right amygdala activation was found when matching perceptually, whereas greater right ventral lateral prefrontal activation was found when matching to labels, and activation of right ventral PFC predicted the activation of the amygdala. These findings have been replicated and extended to other classes of negatively valenced stimuli, including the perception of African-American faces (M. D. Lieberman, Hariri, Jarcho, Eisenberger, & Bookheimer, 2004) and aversive photographs (Hariri et al., 2003), for which inverse relationships between right ventral PFC and right amygdala have been found when participants matched to labels as compared to percepts. As a group, these studies have been taken to suggest that explicit attention to and semantic labeling of emotional properties of stimuli could down regulate amygdala responses to them. A potential problem for this account, however, is that the perceptual condition in which more amygdala activation is observed includes three faces as compared to the single face presented in the labeling condition, which means that it is difficult to determine whether number of face stimuli or the nature of the judgment is what drives the apparent amygdala modulation. The fact that amygdala activation inversely correlates with the right ventral PFC activation only when participants label African-American faces argues against this account, however (M. D. Lieberman et al., 2004).

Be that as it may, explicit labeling of the affective properties of stimuli has been shown to down-regulate amygdala activation in three other paradigms, all of which equate stimulus properties in the affective labeling and non-labeling conditions. The first is a variant of the

priming paradigm of Murphy and Zajonc in which supraliminally presented target faces with weak expressions of anger were preceded by subliminal primes that were angry faces, neutral faces, or blank control stimuli (Murphy & Zajonc, 1993; Nomura et al., 2004). Participants judged whether the consciously perceived target face seemed to be angry, happy, or neutral. In general, greater right amygdala activation was observed for trials with angry primes, and right amygdala activation was correlated with the tendency to judge the target face as angry, whereas right ventral lateral PFC showed precisely the opposite pattern -with activation inversely correlating both with amygdala activity and attributions of angry expressions. In the second, decreased amygdala activation was observed by Taylor et al. when participants rated the valence of aversive and neutral photographs as compared to viewing them passively (Taylor, Phan, Decker, & Liberzon, 2003). And in the third, Critchley et al. had participants view happy, angry, or neutral faces, and judged either face gender or judged whether or not each face was emotionally expressive (Critchley et al., 2000). In general, perception of emotional as compared to neutral faces activated the left amygdala, and strikingly, right amygdala activation was diminished for explicit emotion as compared to gender judgments.

Although all of these studies are consistent with the notion that explicit semantic labeling of emotional properties of stimuli can down regulate amygdala responses - and presumably negative affect as well - there are two salient problems with this account. The first is that this account cannot explain why retrieving semantic emotion knowledge and labeling affective properties of stimuli can sometimes boost negative affect as well as amygdala activation (Ochsner et al., 2004), as mentioned above. The second is that a number of studies have failed to observe modulation of amygdala responses when participants explicitly attend to or semantically label affective stimulus properties.

For example, Gorno-Tempini et al. (2001) had participants judge either the gender or emotional expression of happy, disgust, or neutral faces. Although left amygdala activation generally was found for emotional faces, explicit expression judgments were not reported to diminish amygdala activation, and instead activated right dorsolateral PFC. It should be noted, however, that because the authors did not report the gender > expression judgment contrast, it is difficult to determine whether gender judgments might have produced greater amygdala activation, as was observed by Critchley et al. (2000). This ambiguity of analysis was not a problem for Winston et al., who morphed happy, sad, disgust, and fear faces with neutral faces to produce stimuli with high and low intensity expressions, presented these stimuli in pairs, and asked participants to judge either which face of each pair was more male, or which face was more emotionally expressive (Winston, O'Doherty, & Dolan, 2003). Although increasing intensity of expression activated the amygdala bilaterally, in contrast to the results of Critchley et al. (2000), amygdala activation did not vary with judgment type. In a similar study with different stimuli, this time using normatively trustworthy as compared to untrustworthy appearing neutral faces (that would be judged as nevertheless expressing a high degree of anger), Winston et al. had participants either judge whether faces were of high school or university students, or whether they were trustworthy or untrustworthy individuals (Winston, Strange, O'Doherty, & Dolan, 2002). Bilateral amygdala activation to untrustworthy faces was observed that once again did not vary as a function of judgment type. And finally, Cunningham et al. had participants judge whether photos of famous people had been taken in the past or present or represented good (e.g. Martin Luther King) or bad (e.g. Osama bin Laden) people (W.A. Cunningham et al., 2003). "Bad" as compared to "good" individuals activated the left amygdala and right ventral PFC, and amygdala activation did not vary as a function of judgment type.

If semantic selection/labeling sometimes results in the modulation of affective evaluation and amygdala activation, but not always, what determines when this modulation will take place? One possibility, suggested earlier in the context of attentional gating, is that regulatory interactions between PFC and the amygdala take place when one has the explicit motive or goal to regulate one's evaluative responses to stimulus dimensions that are in the focus of attention. This is certainly the case when participants are instructed to regulate, as demonstrated by the fact that all of the reappraisal studies have shown relative amygdala deactivation, and all involved attention to, and the explicit goal-directed regulation of, affect. But it is also the case that even when not explicitly instructed to control one's evaluation, participants may spontaneously do so, and some of the cross-study variability could result from participants having the motivation to control in some experiments, but not in others (Erber, 1996). This possibility has been strongly supported by a study from Cunningham et al. whose participants judged whether words were either a) abstract or concrete, or b) whether they represented good or bad attitude objects. After the scanning session, participants rated each word for affective intensity, good/bad valence, and their motive to control their evaluations of the attitude object (W. A. Cunningham, Raye, & Johnson, in press). When these ratings were used to predict brain activation to attitude objects during each judgment task, it was found that in general, affectively intense words produced left amygdala activation, and critically, that when making good/bad judgments, the motive to control predicted activation of the anterior cingulate, right orbitofrontal cortex and lateral PFC, with activation of the latter predicting amygdala deactivation.

Conclusions and Future Directions

The overarching question motivating this chapter has been: what are the neurocognitive mechanisms by which thinking controls negative feeling? In the final section of this chapter we

pause to take stock of what the preceding reviews suggests as an answer, or answers, to this question, and include by highlighting specific questions that have yet to be addressed.

What answers have emerged?

It doesn't take a neuroimaging study to tell us that distraction, inattention, reappraisal, or alterations of construal more generally, can change the way we affectively evaluate a stimulus. Careful behavioral observation and empirical experimentation, as well as good old-fashioned first-person experience, have long since confirmed this fact. What neuroimaging studies have begun to reveal, however, are the mechanisms that underlie these changes in affective construal. Three consistent findings have emerged that can be taken as answers to the question of what mechanisms mediate the cognitive regulation of affect.

1. Interactions between prefrontal and cingulate systems that implement control processes, and amygdala, cingulate, and other systems that implement affective appraisal processes, underlie the cognitive control of affect. This starting hypothesis, built by analogy to "cold" forms of cognitive control, has been supported in studies of distraction during pain, reappraisal, and selective evaluation of the affective properties of stimuli.
2. The simplest alternative explanation for the effects of cognitive control upon affective processing – namely that simply engaging in cognitive processing, or thinking, diminishes affective evaluation in the same way that attending to a sound dampens vision - cannot account for the available data. If this account were correct, then amygdala activation should always decrease whenever participants perform some type of judgment, which clearly is not the case - amygdala activation can remain invariant with respect to variations in attention (e.g. Anderson et al., 2003) and judgment (Winston et al., 2002, 2003), and can be maintained (Schaefer et al., 2002) or even increase for some types of judgment (Ochsner et

al., 2004).

3. The down-regulation of negative affect by manipulation of the meaning of a stimulus may involve predominantly right lateralized systems. This inference is supported by a number of studies showing an inverse relationship between right ventral lateral PFC/OFC and right amygdala during the conscious (and likely regulated) as opposed to nonconscious (and likely unregulated) perception of black faces (W.A. Cunningham et al., in press), during reappraisal (Beauregard et al., 2001; Levesque et al., 2003; Ochsner et al., 2004), and during the selective evaluation of the explicit affective properties of faces (Hariri et al., 1999; Lieberman et al., 2004; Nomura et al., 2004) or words representing attitude objects (W. A. Cunningham et al., in press).
4. The mechanisms mediating the regulation of experience and the regulation of perception/judgment may be highly overlapping. Virtually all of the studies investigating reappraisal instruct participants to change the way they feel about a stimulus by changing the way in which they make judgments about it. Virtually all of the studies involving the selective evaluation of affective as compared to not affective properties of stimuli do not make reference to experience in any way, instructing participants simply to attend to and discriminate stimulus features. Both of these forms of meaning manipulation rely on right PFC/OFC regions to mediate their regulatory impact upon an affective outcome - experience in one case, judgment in the other - which are correlated with amygdala activation in both cases. It should be noted, however, that one reason regulation of experience and perception may recruit similar mechanisms is because most tasks have involved both types of regulatory processing, and have failed to discriminate them cleanly.

<u>What questions remain outstanding?</u>

Research on the neurocognitive mechanisms of affect regulation has only been a primary focus of functional imaging research for the past 5-10 years, so it is perhaps not surprising that the list of questions yet to be addressed is longer than the list of emerging answers.

1. Although some of the primary neural players in the cognitive regulation of affect have been identified, the precise functional nature of their regulatory interactions with the amygdala (or other affective appraisal systems) remain to be clarified, and may be context/task sensitive. Increased prefrontal/cingulate and decreased amygdala activation could result from at least two types of regulatory mechanisms: 1) processes involved in selecting appropriate, and/or limiting conflict between inappropriate, responses - processes that have been linked to right ventral PFC and anterior cingulate (Miller and Cohen, 2001), or 2) alterations in input to the amygdala that either 2a) cut off or limit the flow of perceptual information indicating the presence of an aversive stimulus, as may be the case for dividing attention and selected evaluation, or 2b) mentally generate an alternative set of semantic and/or perceptual inputs that feed forward to the amygdala indicating the presence of a more neutral stimulus, as may be the case for both reappraisal and selective evaluation. It remains for future research to design studies that manipulate the psychological factors involved in a given task to discriminate these possibilities, which likely will include manipulations of both judgment and stimulus variables.
2. A second related question concerns the way in which different types of strategies may involve different types of regulatory interactions. Distraction as compared to reappraisal, for example, may recruit different systems but because extant studies of distraction have involved pain, studies of reappraisal have involved affectively charged photographs, and no published studies have compared both strategies in a single task, it is difficult to address this

question. Another variable that may be important concerns the stimulus content that is in the focus of attention or is the focus of the reappraisal strategy. Strategies that involve an inward focus upon oneself and one's emotional experience may recruit medial prefrontal regions, as suggested by studies showing medial PFC activation for self-focused reappraisal strategies asking participants to psychologically distance themselves from pictured events (Ochsner et al., 2004) and for the regulation of pain experience (Bantick et al., 2002; Frankenstein et al, 2001; Valet et al., 2004) as opposed to studies showing lateral PFC activation for reappraisal strategies focused on situational features (Ochsner et al., 2004) and tasks involving selective evaluation of affective stimulus properties (e.g. Cunningham et al., 2003; Hariri et al., 1999, 2003; Lieberman et al., 2004).

3. To what extent must the conscious goal or motive to regulate be present in order for regulatory effects on the amygdala to be observed? Studies that explicitly have given the participants the conscious goal to regulate (e.g. Ochsner et al, 2002; 2004) or have measured their spontaneous tendency to regulate (W. A. Cunningham et al., in press) have consistently observed amygdala deactivation, whereas other studies that neither manipulate nor measure explicit regulatory goals less consistently have observed amygdala modulation. The simple fact that in everyday life thinking often influences feeling without our having the explicit intent for this to happen makes it seem unlikely that modulation always requires the conscious goal to change how one feels or perceives the world. What kind of processing goal is necessary is not yet clear, however.
4. Are the same control mechanisms and regulatory interactions involved in attention gating, meaning manipulation, and response modulation? In order to address this question, different types of strategies would have to be compared within the context of the same experiment,

using the same participants and stimuli for each type of regulatory intervention. No published studies have examined the neurocognitive substrates of an explicitly behavior-focused affect regulation strategy, such as the suppression of emotion expressive behavior (J. J. Gross, 1998a).

5. To what extent are regulatory dynamics like those described here also involved in other types of cognition-affect interactions not typically described as emotion-regulatory that nonetheless involve the use of cognitive control to modulate affective responses in various ways? Stimulus-reward reversal tasks and decision-making tasks, for example, may involve attention gating and meaning manipulation processes like those involved in the experiments described here. Brain imaging studies could be used to determine whether similar or different mechanisms are involved. Expectations and beliefs also influence affect. Recent studies of the placebo effect suggest, for example, that prefrontal and anterior cingulate regions like those involved in reappraisal may modulate pain-related activations of the mid cingulate cortex. Future studies could directly compare reappraisal and placebo to determine whether or not they depend upon similar mechanisms.
6. To what extent are the mechanisms mediating affect regulation similar to, or different than, mechanisms mediating regulation of nonaffective inputs, including linguistic, visual spatial, and auditory information? In other words, to what extent are the systems classically thought to mediate shifts of spatial attention (Posner & Rothbart, 1998), working memory (D'Esposito, Postle, & Rypma, 2000) or response inhibition (Braver, Barch, Gray, Molfese, & Snyder, 2001) like those involved in regulating an affective response? Their similarities are differences could eliminate the nature of the mechanisms involved in each.
7. How do individual differences in the tendency to generate affective responses of particular

kinds, the ability to control, and other personality or mood-related variables, impact the way in which affect regulation systems operate? This broad question may include specific questions about the development of regulatory capacity in children, its evolution across the lifespan as we age, its breakdown in individuals suffering from psychiatric disorders, as well as the range of variability found in normal healthy populations (J. J. Gross, & John, O.P., 2002). Our models of the functional architecture of affect regulation will be stronger to the extent that they can accommodate, and make predictions about, the way in which specific neural mechanisms may differentially contribute to emotional responding and regulatory success in different individuals (Kosslyn et al., 2002).

Concluding comment

The capacity Marcus Aurelius identified over two millennia ago - for our estimates of the value of a situation to determine our affective response to it - is central to our ability to adapt to stressful circumstances, and a complete understanding of the mechanisms that give rise to this capacity is essential. A premise of this chapter is that a very useful kind of explanation speaks to multiple levels analysis, linking socioemotional experience and behavior to theories of information processing mechanisms, and linking those theories of mechanism to descriptions of underlying neural systems (J. T. Cacioppo, Berntson, Sheridan, & McClintock, 2000; Ochsner & Lieberman, 2001). In doing so, brain data can constrain theories of psychological process, and vice versa. Although this chapter has focused on data from functional neuroimaging studies, the use of multiple other neuroscience techniques (including scalp electrode recording and neuropsychological patients analysis) to converge upon theories consistent with multiple methodologies is essential and necessary. With any luck, in the next decade our estimate of the progress we've made in characterizing the functional architecture of affect regulation will

produce no pain and all, but a great deal of pleasure.

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