CHAPTER 9

CinguloAmygdala Interactions in Surprise and Extinction: Interpreting Associative Ambiguity

Jonathan A. Oler, Gregory J. Quirk, and Paul J. Whalen

Chapter contents

Many chapters in this volume depict the anterior cingulate cortex (ACC) as a heterogeneous structure involved in the processing of both cognitive and emotional information. A vast animal and human literature supports the notion that the amygdala is a critical structure in the processing of emotional information. Given the strong reciprocal connectivity between the ACC and the amygdala, any assessment of the role of the ACC in the processing of emotional information would benefit from careful consideration of cinguloamygdala interactions. To this end, we explore the relation between electrophysiological data recorded from the rodent brain and functional neuroimaging data gleaned from studies in humans. Taken together, these data reveal a specific role for cinguloamygdala processing in the interpretation of emotional information, especially when the predictive value of biologically relevant stimuli is ambiguous.

Goals of This Chapter

We begin by briefly describing the anatomical connections between the ACC, the anterior midcingulate cortex (aMCC), and amygdala; the reader is referred to Chapter 6 for a more thorough review of amygdalocingulate circuits. We then consider studies of extinction learning in animal subjects that have delineated a particularly compelling relationship between the subgenual ACC and the amygdala. Finally, human neuroimaging reports

of cinguloamygdala interactions are reviewed that provide data consistent with the animal work. We find that amygdala responsivity to biologically relevant stimuli can routinely come under regulatory control of the ACC and aMCC. This chapter has the following specific goals:

1 Describe the reciprocal connectivity between ACC and different nuclei in the amygdala.

2 Provide a summary of experimental data on extinction learning and single-unit recordings in rat ACC.

3 Summarize fMRI observations in human subjects showing that a similar "extinction-like" ACC-amygdala circuitry is activated in human subjects when viewing faces with surprised expressions.

4 Evaluate the relationship between these data sets derived from disparate sources.

5 Provide a clear definition of associative ambiguity, and consider a hypothesis that reconciles these cross-species results.

Anterior Cingulate and Midcingulate Reciprocal Connections with Basolateral Amygdala

The anatomy and connectivity of the amygdala has been reviewed for the primate (Amaral *et al.*, 1992; Chapters 6 and 15) and the rat (Pitkänen, 2000). An extensive animal literature has generated compelling evidence that the basolateral amygdala nuclei (lateral, basal, accessory basal; BLA) can be behaviorally, chemoarchitectonically, and ontogenetically dissociated from amygdala sub-structures such as the corticomedial nucleus and central nucleus/extended amygdala (Hatfield *et al.*, 1996; Killcross *et al.*, 1997; Amorapanth *et al.*, 2000; Davis and Whalen, 2001; Gallagher, 2000; Swanson and Petrovitch, 1998; Alheid, 2003). A functional model of the amygdala that has proven useful offers the lateral nucleus as a sensory input structure, the basal nuclei as convergent processing areas, and the central nucleus (Ce) as the origin of descending output to autonomic and visceral targets (Ledoux *et al.*, 1990; Pitkänen *et al.*, 1997; Ledoux, 1996). However, numerous anterograde and retrograde tract-tracing studies have revealed extensive projections originating in the BLA to frontal, insular, anterior cingulate, visual, and parahippocampal cortices (Krettek and Price, 1977; Mcdonald, 1991; Ghashghaei and Barbas, 2002; Mcdonald, 1987; Sripanidkulchai *et al.*, 1984; Amaral and Price, 1984; Petrovich *et al.*, 1996; Barbas and De Olmos, 1990; Conde *et al.*, 1995; Sarter and Markowitsch, 1984; Kita and Kitai, 1990; Bacon *et al.*, 1996; Pitkänen *et al.*, 2000; Freese and Amaral, 2005). Thus, though the Ce has a widespread (primarily descending) projection system (Davis, 2000), the BLA has an ascending projection system of its own, and the ACC is one of its major targets.

The amygdalofugal projections targeting the ACC and aMCC of the monkey originate primarily in the basal and accessory basal nuclei, and most heavily innervate areas 25, 24, and 32 (Amaral *et al.*, 1992; Chapter 6). The terminal fields of these ACC projecting amygdaloid axons are seen primarily at the border between layer I and II, as well as within layers V and VI (Amaral and Price, 1984). These projections are most likely excitatory in nature, as the typical projection neuron of the BLA is the glutamatergic pyramidal cell (Mcdonald, 1992). In fact, a recent study looking at hippocampal–amygdala interactions in the anesthetized rat observed short latency excitatory responses in ACC neurons following electrical stimulation of the BLA (Ishikawa and Nakamura, 2003). However, electrical stimulation of the BLA in the rat can also inhibit the activity of ACC neurons (Ishikawa and Nakamura, 2003; Perez-Jaranay and Vives, 1991), which is perhaps indicative of a feed-forward inhibition.

The ACC projections to the amygdala arise from neurons in areas 24, 32, and 25 (Mcdonald, 1998). Although primarily observed in the BLA, tract-tracing studies in the rat and cat have shown widespread ACC termination in the amygdala, while the projections appear to be restricted to the magnocellular subdivisions of the basal and accessory basal nuclei in the primate (Cassell and Wright, 1986; Mcdonald *et al.*, 1996; Mcdonald, 1998; Stefanacci and Amaral, 2002; Pandya *et al.*, 1981; Chiba *et al.*, 2001; Carmichael and Price, 1995; Ottersen, 1982; Hurley *et al.*, 1991; Sesack *et al.*, 1989; Takagishi and Chiba, 1991; Aggleton *et al.*, 1980; Russchen, 1982; Pandya *et al.*, 1973). Electron microscopic investigation of the synaptology of the ACC projection to amygdala found that these afferent terminals form asymmetric synapses primarily on dendritic spines (Brinley-Reed *et al.*, 1995), indicative of an excitatory ACC input to the BLA. In fact, electrical stimulation of area 32 (PL) and area 25 (IL) in the rat excites inhibitory interneurons within BLA (Rosenkranz and Grace, 2001) and reduces the excitability of Ce output neurons (Quirk *et al.*, 2003), which again suggests a feed-forward inhibitory circuitry. Similarly, chemical stimulation of the area 25/IL activates GABAergic intercalated cells in the amygdala, which inhibit BLA projections to the Ce (Barrett *et al.*, 2003). Some fibers from the ACC also appear to terminate in the substantia innominata and extended amygdala (Aggleton *et al.*, 1980; Mcdonald *et al.*, 1999). Thus, the ACC has the greatest reciprocal connectivity with the amygdala when compared to MCC.

The nomenclature used to delineate regions of the frontal lobe varies across species, and the analogous regions of the ACC in the rat are shown in Chapter 3. Area 32 is also referred to as PL and area 25 as IL

(Mcdonald *et al.*, 1996). Here we refer to area 25/IL, areas 32/PL, and area 24. The direct analogies of the rodent, monkey, and human areas in terms of the modified Brodmann nomenclature are available in Chapter 3.

ACC-Amygdala and Fear Extinction: Electrophysiological and Behavioral Studies

The amygdala is necessary for the acquisition and expression of learned fear associations (Ledoux, 2000; Davis and Whalen, 2001; Maren and Quirk, 2004). Typically, animals learn to fear a conditioned stimulus (CS) that predicts an unconditioned stimulus (US). During auditory fear conditioning for example, following several tone-footshock pairings rats will freeze when the tone is later presented alone (Quirk *et al.*, 1995; Oler and Markus, 1998; Kim and Fanselow, 1992). Thalamic and cortical afferents communicate CS and US information to BLA (Romanski and Ledoux, 1992; Li *et al.*, 1996; Ledoux *et al.*, 1987; Shi and Cassell, 1998), where CS–US associations are thought to be formed (Rogan *et al.*, 1997; Fanselow and Ledoux, 1999). The behavioral and autonomic expression of conditioned fear, however, is thought to result from excitatory influences of the BLA on the coordinated efferent systems of Ce (Davis, 2000).

When the tone CS is repeatedly presented in the absence of the US, the conditioned response will rapidly diminish, a phenomenon known as extinction (Pavlov, 1927). Behavioral studies have demonstrated that extinction does not expunge the CS–US association, but rather a new memory trace is formed, one that inhibits the previously established conditioned response (Quirk, 2002; Rescorla, 2001). The fact that extinction learning requires N-methyl-D-aspartic acid (NMDA) receptors, and is facilitated by NMDA receptor agonists, further supports the idea that extinction is much more than simple forgetting (Falls *et al.*, 1992; Walker *et al.*, 2002; Santini *et al.*, 2001). After extinction, therefore, the CS is inherently ambiguous, potentially predicting either shock or the absence of shock. This ambiguity is especially pronounced when the CS is administered in the context where both conditioning and extinction training occurred (Milad and Quirk, 2002; Quirk *et al.*, 2000).

Relevant to the present discussion is the fact that lesions of the area 32/PL in rats prolong the extinction of a conditioned fear response to an explicit CS (Morgan *et al.*, 1993), while lesions of area 25/IL have little effect on the process of conditioning or extinction (Quirk *et al.*, 2000), but instead affect the ability to use this information when these stimuli are encountered in the future. For example, while neurons of area 25/IL are not responsive to a tone CS during conditioning or extinction training, these same cells show robust CS-evoked firing when the animal is recalling extinction the following day (Milad and Quirk, 2002). The relative change in CS-evoked activity of these area 25 neurons correlates with the behavioral expression of extinction as shown in Figure 9.1. Similar findings in prefrontal cortex have been reported with evoked potentials (Herry and Garcia, 2002) and metabolic mapping techniques (Barrett *et al.*, 2003). Thus, the evidence suggests that long-term memory for extinction depends on area 25/IL and this area may be particularly important in regulating the emotional response to previously learned stimuli.

Electrical stimulation of area 25/IL is sufficient to inhibit the expression of a conditioned fear response, mimicking the effects observed following extinction training, and suggesting that the subgenual ACC can regulate the response of the amygdala to fear eliciting stimuli (Milad *et al.*, 2004). Additionally, stimulation of area 25/IL decreases the responsiveness of Ce output neurons to their afferent inputs (Quirk *et al.*, 2003), a phenomenon hypothesized to be mediated through the intrinsic inhibitory networks of the amygdala (Paré *et al.*, 2004). Conversely, activity of area 32/PL is suppressed with increases in the freezing behavior observed in response to an aversively conditioned CS, and ipsilateral lesions of the BLA attenuate this reciprocal relationship (Garcia *et al.*, 1999). The fact that acquisition inhibits, and extinction potentiates ACC activity is consistent with ACC inhibition of conditioned fear. Thus, complex interactions among the rat area 32/PL (pregenual ACC), area 25/IL (sACC), and amygdala mediate fear extinction learning and expression.

Imaging Studies of CinguloAmygdala Interactions

Neuroimaging studies employing functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are beginning to reveal the relationships and functional architecture of emotion and its expression in humans (Davidson and Irwin, 1999). The ACC can be subdivided (based on behavioral, electrophysiological, and imaging data) into a "cognitive" division (aMCC) and an "affective" division (ACC; Bush *et al.*, 2000; Devinsky *et al.*, 1995). In a meta-analysis of imaging studies of ACC function, Bush *et al.* (2000) convincingly demonstrate that cognitively demanding tasks (i.e., Stroop tasks, divided-attention tasks, response-selection tasks and working-memory tasks) produce activations that cluster in the aMCC, while affect-related tasks (i.e., emotional faces, symptom provocation) generate activations that cluster in the ACC. Indeed, this dichotomy in ACC function was observed within the same subjects across two studies

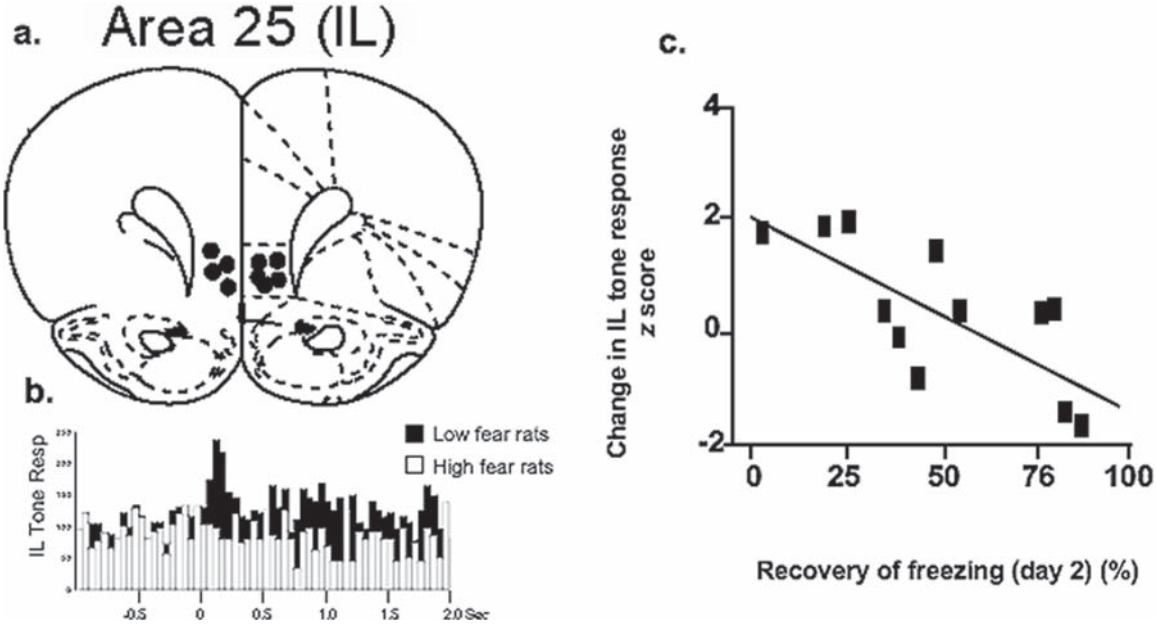

Fig. 9.1 Area 25/IL tone responses are correlated with spontaneous recovery of freezing after extinction. A. Recording sites in Area 25/IL. B. Group PSTHs showing tone responses of neurons from high-recovery (12 cells) and low-recovery (19 cells) groups on day 2. The bin size was 50 ms. C. Scatter plot showing the change in tone response across days versus the percentage recovery of freezing on day 2. Firing rate 0–400 ms after tone onset was compared to pre-tone baseline rate with z-score. Each point represents the averaged response of all recorded neurons in each rat (Milad and Quirk, 2002).

(Bush *et al.*, 1998; Whalen *et al.*, 1998). Each study employed one of two Stroop-like interference tasks with differing causes of interference (i.e. one "cognitive" and one "affective"). During the cognitive version of the task (the counting Stroop), sets of up to four vertically tiled words appeared on a screen. Subjects were instructed to press a button corresponding to the number of words in each set, regardless of their meaning. Interference trials contained number words that were incongruent with the correct response (e.g. 'three' written four times). During the interference portion of the affective version of the task (the emotional counting Stroop), emotionally laden words were substituted for the number words (e.g. 'murder' written four times). Emotionally neutral words were used for comparison. As nicely depicted by Bush *et al.* (2000, Box 1, p. 218 and in Chapter 12), the cognitive version of the task activated the aMCC and the emotional version of the task activated pACC.

Neurons in the ACC and amygdala respond to both positive and negative events, stimuli that predict these events, and the devaluation or reversal of these predictive contingencies (Baxter *et al.*, 2000; Saddoris *et al.*, 2005; Rolls, 1999; Chapter 8). In this context it should be noted that reversal learning is also critically dependent upon the adjacent orbital prefrontal cortex. Thus, interactions between these regions may be especially important for response to a change in the predictive meaning of a presented stimulus, consistent with the modulatory role the sACC appears to play in extinction (Morgan *et al.*, 1993; Quirk *et al.*, 2000). Numerous studies suggest that sensory stimuli demonstrating some predictive validity in terms of biological import (e.g., possible threat) appear sufficient to engage the amygdala, even though these stimuli may not evoke high levels of arousal (Whalen, 1998). Pictures of fearful facial expressions are a good example of such stimuli (Ekman and Friesen, 1976). An intact amygdala facilitates the perception of fear in a face (Adolphs *et al.*, 1994; Adolphs *et al.*, 2005), and fearful faces are routinely used to activate the human amygdala in the scanner (Whalen *et al.*, 2001). Indeed, though a portion of the amygdaloid complex (dorsal amygdala) is likely sensitive to the fact that fearful expressions leave the source of their elicitation ambiguous (see Whalen, 1998; Whalen *et al.*, 2001 for discussion), robust amygdala activation observed within the ventral amygdala (BLA) is likely due to unanimous agreement across subjects that fearful expressions are negatively valenced (Kim *et al.*, 2003). Given the hypothesis that cinguloamygdala circuits subserve valence calculations during extinction training, one way to observe increased cinguloamygdala interaction in an imaging study of facial expression would be to select an expression with unclear valence.

Facial Expression of Surprise

Surprised expressions provide an important comparison expression for fear. Though neither expression (fear or surprise) indicates the exact nature of their eliciting event, fearful expressions do provide additional information concerning the predicted negative valence. Surprise, on the other hand, can be interpreted either positively or negatively (Tomkins and Mccarter, 1964). For example, a surprised expression might be observed in response to an oncoming car (negative) or an unexpected birthday party (positive). Thus, surprised facial expressions can be used to reveal important individual differences in both a) the propensity to subjectively ascribe positive or negative valence to an ambiguous stimulus and b) the relationship between these subjective ratings and fMRI signal changes in the amygdala and ACC.

Indeed, a recent neuroimaging study showed that the relative differences in the level of sACC and amygdala signal changes to surprised versus neutral faces were related to a given subject's interpretation of ambiguously valenced surprised faces as negative or positive (Kim *et al*., 2003). Valence ratings (i.e., 1 = very positive, 9 = very negative) of surprised facial expressions were positively correlated with fMRI responses to surprised versus neutral faces in the right amygdala. That is, more negative interpretations of surprised faces were associated with amygdala signal levels that were higher to surprised faces (compared to neutral), while more positive interpretations were associated with lower signal levels (compared to neutral). Voxels displaying this correlation were located within the anterior, lateral, and ventral amygdala, within the confines of the BLA region in the human (Mai *et al*. 2003). No significant correlation was observed within the left amygdala.

In this same study, areas 25 and 32 in sACC displayed the opposite relationship with valence ratings of surprised faces (compared to amygdala). Figure 9.2 presents voxels within the sACC where more positive interpretations of surprised faces were associated with signal levels that were higher to surprised faces (compared to neutral), while more negative interpretations were associated with lower signal levels (compared to neutral). To summarize the results, a region of right ventral amygdala and bilateral regions of sACC showed an inverse relationship with valence ratings of surprised faces. Accordingly, evidence of functional connectivity between these regions in response to surprise was also observed. That is, there was a significant inverse correlation between signal changes within amygdala and these sACC loci. Figure 9.3 presents a categorical breakdown of the percent signal-change data based upon subjective valence ratings offered by the subjects. Thus, it is the case that subjects who offered more negative ratings showed higher amygdala and lower ACC signal intensities, while subjects offering more positive interpretations showed the inverse pattern.

Other structures that correlated with ratings of surprised expressions are clear candidates for inclusion in a greater circuitry involved in the assessment and/or

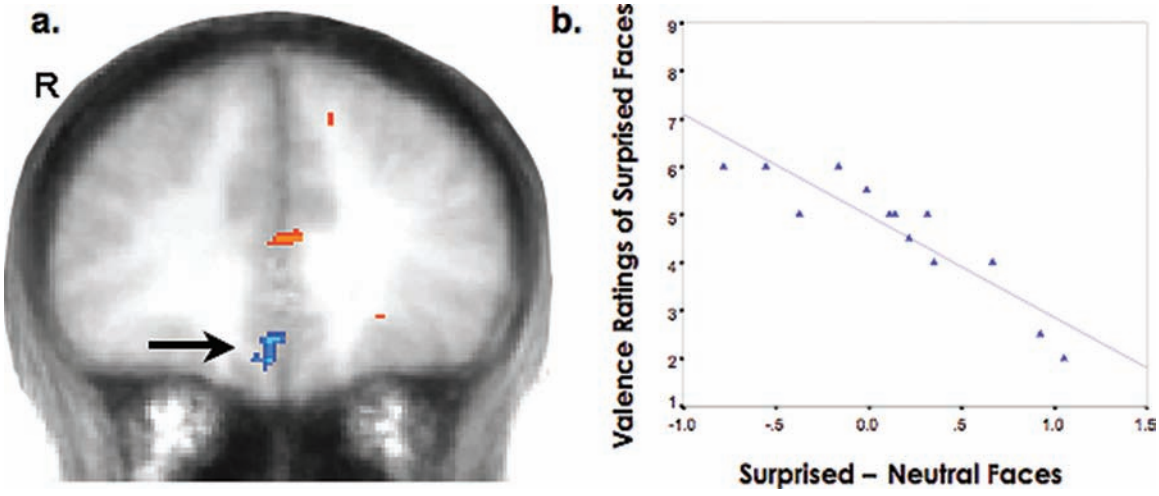

Fig. 9.2 Subgenual ACC signal changes to surprised faces vary as a function of individual differences in the interpretation of these expressions. A. fMRI signal change to surprised versus neutral faces (activations thresholded at $p < 0.01$ and superimposed on T1-weighted high-resolution anatomical images averaged across all subjects). R = right. B. In the graph, the ordinate presents fMRI signal change to surprised versus neutral faces for the ACC cluster depicted with an arrow. The abscissa presents the valence rating scale from 1 - 9. 1 = very positive, 3 = positive, 5 = neither negative nor positive, 7 = negative, 9 = very negative. Thus, greater activation of sACC is observed to a positive interpretation of the predictive stimulus (similar to an extinguished tone-CS, see Fig. 9.1).

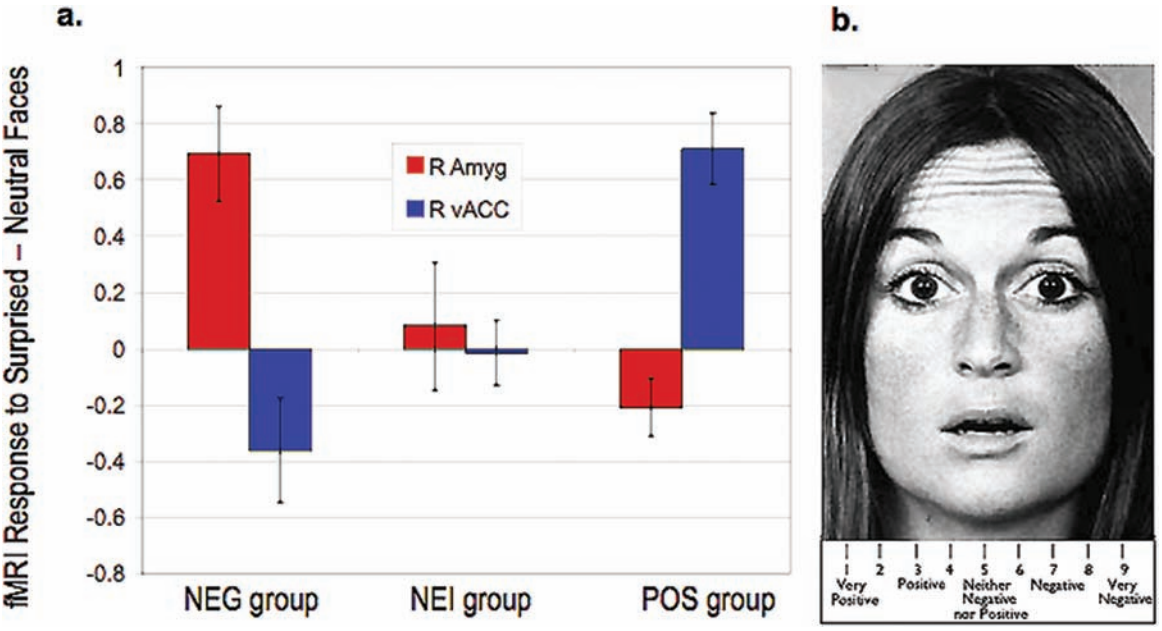

Fig. 9.3 The amygdala and the sACC display an inverse functional relationship. A. The bar graph shows the fMRI response for the regions in Kim ***et al***. (2003) while subjects viewed blocks of surprised and neutral faces (surprised – neutral). The red bars depict the levels of activation in the right amygdala, and the blue bars activation of the right ventral ACC (see Fig. 9.4 for loci). Subjects who rated the surprised faces as "negative" showed increased amygdala response and decreased activity in sACC. Subjects rating the same stimuli as "positive" displayed the opposite pattern of brain activity. Subjects who rated the faces a "neither positive nor negative" produced fMRI changes that were not significantly different from baseline in either structure. NEG = negative, NEI = neither positive or negative, POS = positive. B. An example of one of the surprised faces used in this task. Reprinted with permission from Ekman and Friesen, (1976).

determination of their valence. Specifically, aMCC, like the amygdala, showed a positive correlation with valence ratings (this locus is visible in Figure 9.4, dorsal to the sACC locus). These cingulate voxels also showed evidence of functional connectivity with the activated amygdala voxels, showing a positive relationship. This finding may be relevant to previous studies discussed above, demonstrating complementary but separate roles for aMCC and sACC in the evaluation of predictive biologically relevant stimuli. The aMCC locus showing a positive correlation with valence ratings (as well as amygdala response) is consistent with the locus showing responsivity to affectively laden words during the emotional Stroop task (Whalen *et al*., 1998).

The three activations depicted in Figure 9.4 were identified in terms of their correlations with ratings of surprised facial expression blocks; the amygdala and aMCC demonstrated positive correlations with these ratings, while the sACC showed a negative correlation. It is important to note that these activations represent final averaged relationships after numerous presentations of surprised faces. Thus, though they offer evidence of functional connectivity, they do not necessitate direct connectivity, and they tell us little about the nature (e.g., excitatory, inhibitory, etc.), direction (amygdala to ACC, or the reverse, etc.), order (which areas respond first, how do they change over time), or weighting (are some connections 'heavier' or more prominent in determining this behavioral effect) of

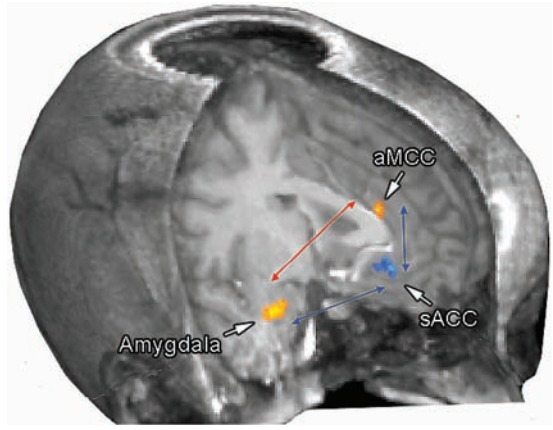

Fig. 9.4 Three-dimensional reconstruction showing the loci of activation revealed in Kim ***et al***. (2003) produced by voxel-wise correlations with surprised faces valence ratings. The amygdala and aMCC were positively correlated with the valence ratings, while the sACC was negatively correlated with the same ratings. Red arrow indicates a positive correlation between loci of activation, and blue arrows indicate negative correlations between loci.

these putative connections. Still, they are consistent with models of prefrontal-limbic regulation (Baxter *et al*., 2000; Damasio, 1994; Morgan *et al*., 1993; Quirk *et al*., 2000; Rolls, 1999; Schoenbaum *et al*., 1999), they parallel the animal extinction literature, and they provide candidate structures that can be investigated in future studies. In fact, fMRI studies of fear conditioning and extinction learning in humans reveal similar activations through these regions of cingulate cortex and the amygdala (see Figures 2b and 3a in Phelps *et al*., 2004).

The animal and human data described above leads us to the following working hypothesis: upon encountering the expression of surprise, the amygdala initially sends a "first pass" message categorizing these faces as "potentially threatening" in all subjects (Halgren, 1992; Ledoux, 1996; Davis and Whalen, 2001). The ACC, based upon additional inputs from multiple brain regions providing information about past experiences or present context, could then communicate alternative hypotheses back to the amygdala, including the "potential positivity" of these faces. Thus, individual differences in the strength of this ACC "override" message would account for the final averaged inverse differences in signal level observed between the amygdala and sACC.

CinguloAmygdala Interactions in Resolving Biologically-Relevant Ambiguity

Resolving *associative* ambiguity is a complex process requiring access to memory, temporal contexts, spatial contexts, and visceral contexts in order to make a probabilistic "guess" as to the best course of action. More than simple uncertainty, where one doesn't yet have a working hypothesis about predicted outcomes, the term 'associative ambiguity' very specifically refers to a situation where a given predictive stimulus, based upon prior learning, has more than one potential meaning. Here we consider the role of cinguloamygdala interactions in determining which valence representation (positive or negative) will be invoked in a particular circumstance. Stimuli with inconsistent reinforcement histories (like extinguished tones and surprised faces) are inherently ambiguous, potentially predicting either a positive or negative outcome, and this cinguloamygdala circuit appears to subserve the calculation and or retrieval of this information.

The ACC is ideally situated for this function given its access to working memory (Goldman-Rakic, 1988), spatial (hippocampal; posterior cingulate cortex) function, visceral inputs, as well as outputs able to override subcortical fear expression centers (Van Hoesen *et al*., 1993). Each of the divergent brainstem autonomic and somatic targets of the amygdala Ce also receives a projection from the sACC, most of which are inhibitory (Vertes, 2004; Hopkins and Holstege, 1978; Smith *et al*., 2000). This arrangement effectively gives the ACC "veto power" over subcortical conditioned responses allowing the organism to respond appropriately based on recent experience.

Failure to resolve associative ambiguity appropriately can lead to pathological outcomes, and the ACC has been implicated in a variety of affective disorders (Drevets *et al*., 1998; Bush *et al*., 1999; Shin *et al*., 2005; Mayberg, 1997; Bishop *et al*., 2004), as well as the genetic predisposition to inappropriate or pathological expression of affect (Pezawas *et al*., 2005; Meyer-Lindenberg *et al*., 2005). For example, posttraumatic stress disorder (PTSD) is characterized by an inability to suppress fear responses to stimuli that were once associated with trauma but now no longer predict danger. Consistent with impaired cortical regulation of the amygdala, PTSD patients show decreased volume (Rauch *et al*., 2003) and decreased activity (Shin *et al*., 2001; Shin *et al*., 2004; Bremner, 2002; Britton *et al*., 2005; Chapter 21) in ACC, coupled with increased amygdala activity (Rauch *et al*., 2000). A similar area of the ventromedial prefrontal cortex (vmPFC) was recently shown to correlate (in thickness) with memory for fear extinction in normal subjects (Milad *et al*., 2005), suggesting that PTSD patients are deficient in the neural circuitry underlying extinction. Thus, similar to those subjects showing a negative bias in the interpretation of surprised faces, subjects with a thin vmPFC tended to interpret conditioned stimuli that had been extinguished (and were therefore ambiguous) as dangerous.

The complementary animal and human findings discussed in this chapter are consistent with a role for ACC in the regulation of amygdala responsivity during the subjective interpretation of ambiguous stimuli. Indeed, these results join a diverse list of experimental paradigms implicating the ACC in regulatory control when stimuli are associatively ambiguous. Associative ambiguity is high following extinction, when conflicting facts about a CS are learned (Labar *et al*., 1998; Bouton, 2002; Barrett *et al*., 2003; Garcia *et al*., 1999; Milad and Quirk, 2002; Morgan *et al*., 1993; Morgan and Ledoux, 1995; Herry and Garcia, 2002). Associative ambiguity is also high during reversal learning, set-shifting, and other situations requiring behavioral flexibility (Bechara *et al*., 1999; Hariri *et al*., 2003; Hariri *et al*., 2000; Beauregard *et al*., 2001; Ochsner *et al*., 2002; Schaefer *et al*., 2002; Dias and Aggleton, 2000; Li and Shao, 1998; De Bruin *et al*., 1994; Fellows and Farah, 2003; Killcross and Coutureau, 2003). Taken together, these studies support the more generalized involvement of frontotemporal

interactions in behavioral flexibility. As more unified theories of limbic function advance, such theories must include a role for cinguloamygdala integration and regulatory control of biologically relevant information processing, particularly when contingencies are ambiguous.

References

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature 433*: 68–72.

Adolphs, R., Tranel, D., Damasio, A. R., Damasio, H. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Lett Nat 372*: 669–672.

Aggleton, J. P., Burton, M. J., Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (*Macaca mulatta*). *Brain Res 190*: 347–68.

Alheid, G. F. (2003). Extended Amygdala and Basal Forebrain. *Ann NY Acad Sci 985,* 185–205.

Amaral, D. G., Price, J. L. (1984). Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J Comp Neurol 230*: 465–96.

Amaral, D. G., Price, J. L., Pitkänen, A., Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In: *The Amygdala*: *Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Aggelton, J P (Ed.). New York, Wiley-Liss.

Amorapanth, P., Ledoux, J. E., Nader, K. (2000). Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. *Nat Neurosci 3*: 74–79.

Bacon, S. J., Headlam, A. J., Gabbott, P. L., Smith, A. D. (1996). Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. *Brain Res 720*: 211–9.

Barbas, H., De Olmos, J (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *J Comp Neurol 300*: 549–71.

Barrett, D., Shumake, J., Jones, D., Gonzalez-Lima, F. (2003). Metabolic Mapping of Mouse Brain Activity after Extinction of a Conditioned Emotional Response. *J Neurosci 23*: 5740–5749.

Baxter, M. G., Parker, A., Lindner, C. C. C., Izquierdo, A. D., Murray, E. A. (2000). Control of Response Selection by Reinforcer Value Requires Interaction of Amygdala and Orbital Prefrontal Cortex. *J Neurosci 20*: 4311–4319.

Beauregard, M., Levesque, J., Bourgouin, P. (2001). Neural Correlates of Conscious Self-Regulation of Emotion. *J Neurosci*, *21*: 165RC.

Bechara, A., Damasio, H., Damasio, A. R., Lee, G. P. (1999). Different Contributions of the Human Amygdala and Ventromedial Prefrontal Cortex to Decision-Making. *J Neurosci 19*: 5473–5481.

Bishop, S., Duncan, J., Brett, M., Lawrence, A. D. (2004). Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci 7*: 184–8. Epub 2004 Jan 4.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biological Psychiatry *52*: 976–86.

Bremner, J. D. (2002). Neuroimaging studies in post-traumatic stress disorder. *Curr Psychiatry Reports 4*: 254–263.

Brinley-Reed, M., Mascagni, F., Mcdonald, A. J. (1995). Synaptology of prefrontal cortical projections to the basolateral amygdala: an electron microscopic study in the rat. *Neurosci Lett 202*: 45–8.

Britton, J. C., Phan, K. L., Taylor, S. F., Fig, L. M., Liberzon, I. (2005). Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biol Psychiatry 57*: 832–840.

Bush, G., Frazier, J. A., Rauch, S. L., Seidman, L. J., Whalen, P. J., Jenike, M. A., Rosen, B. R., Biederman, J. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting stroop. *Biol Psychiatry 45*: 1542–1552.

Bush, G., Luu, P., Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cog Sci 4*: 215–222.

Bush, G., Whalen, P. J., Rosen, B. R., Jenike, M. A., Mcinerney, S. C., Rauch, S L (1998). The counting stroop: An interference task specialized for functional neuroimaging-validation study with functional MRI. *Human Brain Mapping 6*: 270–282.

Carmichael, S. T., Price, J. L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol 363*: 615–641.

Cassell, M. D., Wright, D. J. (1986). Topography of projections from the medial prefrontal cortex to the amygdala in the rat. *Brain Res Bull 17*: 321–33.

Chiba, T., Kayahara, T., Nakano, K. (2001). Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, *Macaca fuscata*. *Brain Res 888*: 83–101.

Conde, F., Maire-Lepoivre, E., Audinat, E., Crepel, F. (1995). Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. *J Comp Neurol 352*: 567–93.

Damasio, A. R. (1994). *Descartes' Error*: *Emotion, Reason, and the Human Brain*. New York, G. P. Putnam's Sons.

Davidson, R. J., Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci 3*: 11–21.

Davis, M. (2000). The role of the amygdala in conditioned and unconditioned fear and anxiety. In: *The Amygdala. A Functional Analysis,* 2nd edition. Aggleton, JP (Ed.) New York, Oxford University Press.

Davis, M., Whalen, P. (2001). The amygdala: vigilance and emotion. *Mol Psychiatry 6*: 13–34.

De Bruin, J. P., Sanchez-Santed, F., Heinsbroek, R. P., Donker, A., Postmes, P. (1994). A behavioural analysis of rats with damage to the medial prefrontal cortex using the Morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation. *Brain Res 652*: 323–33.

Devinsky, O., Morrell, M., Vogt, B. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain 118*: 279–306.

Dias, R., Aggleton, J. P. (2000). Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: differential involvement of the prelimbic-infralimbic and anterior cingulate cortices in providing behavioural flexibility. *Eur J Neurosci 12*: 4457–66.

Drevets, W. C., Ongur, D., Price, J. L. (1998). Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry 3*: 220–*6,* 190–1.

Ekman, P., Friesen, W. V. (1976). Pictures of Facial Affect. Palo Alto, C. A., Consulting *Psychologists Press*.

Falls, W. A., Miserendino, M. J., Davis, M. (1992). Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. *J Neurosci 12*: 854–863.

Fanselow, M. S., Ledoux, J. E. (1999). Why we think plasticity underlying pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron 23*: 229–232.

Fellows, L. K., Farah, M. J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. *Brain 126*: 1830–7.

Freese, J. L., Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J Comp Neurol 486*: 295–317.

Gallagher, M. (2000). The amygdala and associative learning. In: *The Amygdala. A Functional Analysis*, 2nd edition. Aggleton, JP (Ed.) New York, Oxford University Press.

Garcia, R., Vouimba, R. M., Baudry, M., Thompson, R. F. (1999). The amygdala modulates prefrontal cortex activity relative to conditioned fear. *Nature 402*: 294–6.

Ghashghaei, H. T., Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neurosci 115*: 1261–1279.

Goldman-Rakic, P. S. (1988). Topography of Cognition: Parallel Distributed Networks in Primate Association Cortex. *Ann Revi Neurosci 11*: 137–156.

Halgren, E. (1992). Emotional neurophysiology of the amygdala within the context of human cognition. In: *The Amygdala*: *Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Aggelton, JP (Ed.). New York, Wiley-Liss.

Hariri, A. R., Bookheimer, S. Y., Mazziotta, J. C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport 11*: 43–8.

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry 53*: 494–501.

Hatfield, T., Han, J. S., Conley, M., Gallagher, M., Holland, P. (1996). Neurotoxic Lesions of Basolateral, But Not Central, Amygdala Interfere with Pavlovian Second-Order Conditioning and Reinforcer Devaluation Effects. *J Neurosci 16*: 5256–5265.

Herry, C., Garcia, R. (2002). Prefrontal Cortex Long-Term Potentiation, But Not Long-Term Depression, Is Associated with the Maintenance of Extinction of Learned Fear in Mice. *J Neurosci 22*: 577–583.

Hopkins, D. A., Holstege, G. (1978). Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. *Experi Brain Res 32*: 529–547.

Hurley, K. M., Herbert, H., Moga, M. M., Saper, C. B. (1991). Efferent projections of the infralimbic cortex of the rat. *J Comp Neurol 308;* 249–76.

Ishikawa, A., Nakamura, S. (2003). Convergence and Interaction of Hippocampal and Amygdalar Projections within the Prefrontal Cortex in the Rat. *J Neurosci 23*: 9987–9995.

Killcross, S., Coutureau, E. (2003). Coordination of actions and habits in the medial prefrontal cortex of rats. *Cerebral Cortex 13*: 400–8.

Killcross, S., Robbins, T. W., Everitt, B. J. (1997). Different types of fear-conditioned behavior mediated by separate nuclei within amygdala. *Nature 388*: 377–380.

Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport 14*: 2317–2322.

Kim, J. J., Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science 256*: 675–677.

Kita, H., Kitai, S. T. (1990). Amygdaloid projections to the frontal cortex and the striatum in the rat. *J Comp Neurol 298*: 40–9.

Krettek, J. E., Price, J. L. (1977). Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. *J Comp Neurol 172*: 687–722.

Labar, K., Gatenby, J., Gore, J., Ledoux, J., Phelps, E. (1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed trial fMRI study. *Neuron 20*: 937–945.

Ledoux, J. (1996). *The Emotional Brain. The Mysterious Underpinnings of Emotional Life*. New York, Simon & Schuster.

Ledoux, J. E. (2000). Emotion Circuits in the Brain. *Ann Rev of Neurosci 23*: 155–184.

Ledoux, J. E., Cicchetti, P., Xagoraris, A., Romanski, L. M. (1990). The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J Neurosci 10*: 1062–1069.

Ledoux, J. E., Ruggiero, D. A., Forest, R., Stornetta, R., Reis, D. J. (1987). Topographic organization of convergent projections to the thalamus from the inferior colliculus and spinal cord in the rat. *J Comp Neurol 264*: 123–146.

Li, L., Shao, J. (1998). Restricted lesions to ventral prefrontal subareas block reversal learning but not visual discrimination learning in rats. *Physiol Behav 65*: 371–9.

Li, X. F., Stutzmann, G. E., Ledoux, J. E. (1996). Convergent but temporally separated inputs to lateral amygdala neurons from the auditory thalamus and auditory cortex use different postsynaptic receptors: *in vivo* intracellular and extracellular recordings in fear conditioning pathways. *Learning and Memory 3*: 229–242.

Mai, J. K., Assheuer, J., Paxinos, G. (2003). *Atlas of the Human Brain*, San Diego, Elsevier Academic Press.

Maren, S., Quirk, G. J. (2004). Neuronal Signaling of fear memory. *Nat Rev Neurosci 5*: 844–852.

Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *J Neuropsychiatry 9*: 471–481.

Mcdonald, A. J. (1987). Organization of amygdaloid projections to the mediodorsal thalamus and prefrontal cortex: a fluorescence retrograde transport study in the rat. *J Comp Neurol 262*: 46–58.

Mcdonald, A. J. (1991). Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neurosci 44*: 1–14.

Mcdonald, A. J. (1992). Cell types and intrinsic connections of the amygdala. In: *The Amygdala: Neurobiological Aspects of Emotion, Memory, and mental Dysfunction*. Aggelton, JP (Ed.). New York, Wiley-Liss.

Mcdonald, A. J. (1998). Cortical pathways to the mammalian amygdala. *Prog Neurobiol 55*: 257–332.

Mcdonald, A. J., Mascagni, F., Guo, L. (1996). Projections of the medial and lateral prefrontal cortices to the amygdala: A Phaseolus vulgaris leucoagglutinin study in the rat. *Neurosci 71*: 55–75.

Mcdonald, A. J., Shammah-Lagnado, S. J., Shi, C., Davis, M. (1999). Cortical Afferents to the Extended Amygdala. *Ann NY Acad Sci 877*: 309–338.

Meyer-Lindenberg, A., Hariri, A. R., Munoz, K. E., Mervis, C. B., Mattay, V. S., Morris, C. A., Berman, K. F. (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neurosci 8*: 991–993.

Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the Nat Acad Sci*. USA *102*: 10706–10711.

Milad, M. R., Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature 420*: 70–74.

Milad, M. R., Vidal-Gonzalez, I., Quirk, G. J. (2004). Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behav Neurosci 118*: 389–94.

Morgan, M. A., Ledoux, J. E. (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci 109*: 681–8.

Morgan, M. A., Romanski, L. M., Ledoux, J. E. (1993). Extinction of emotional learning: contribution of medial prefrontal cortex. *Neurosci Lett 163*: 109–13.

Ochsner, K. N., Bunge, S. A., Gross, J. J., Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogni Neurosci 14*: 1215–29.

Oler, J. A., Markus, E. J. (1998). Age-related deficits on the radial maze and in fear conditioning: hippocampal processing and consolidation. *Hippocampus 8*: 402–415.

Ottersen, O. P. (1982). Connections of the amygdala of the rat. IV: Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase. *J Comp Neurol 205*: 30–48.

Pandya, D. N., Van Hoesen, G. W., Domesick, V. B. (1973). A cingulo-amygdaloid projection in the rhesus monkey. *Brain Res 61*: 369–73.

Pandya, D. N., Van Hoesen, G. W., Mesulam, M. M. (1981). Efferent connections of the cingulate gyrus in the rhesus monkey. *Experi Brain Res 42*: 319–30.

Paré, D., Quirk, G. J., Ledoux, J. E. (2004). New Vistas on Amygdala Networks in Conditioned Fear. *J Neurophysiol 92*: 1–9.

Pavlov, I. (1927). *Conditioned Reflexes*, London, Oxford University Press.

Perez-Jaranay, J. M., Vives, F. (1991). Electrophysiological study of the response of medial prefrontal cortex. *Brain Res 564*: 97–101.

Petrovich, G. D., Risold, P. Y., Swanson, L. W. (1996). Organization of projections from the basomedial nucleus of the amygdala: a PHAL study in the rat. *J Comp Neurol 374*: 387–420.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., Egan, M. F., Mattay, V. S., Hariri, A. R., Weinberger, D. R. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neurosci 8*: 828–34.

Phelps, E. A., Delgado, M. R., Nearing, K. I., Ledoux, J. E. (2004). Extinction Learning in Humans: Role of the Amygdala and vmPFC. *Neuron*, *43*: 897–905.

Pitkänen, A. (2000). Connectivity of the rat amygdaloid complex. In: *The Amygdala. A Functional Analysis,* 2nd ed. Aggleton, J. P. (Ed.). New York, Oxford University Press.

Pitkänen, A., Pikkarainen, M., Nurminun, N., Ylinen, A. (2000). Reciprocal connections between amygdala and hippocampal formation, perirhinal cortex, and postrhinal cortex in the rat. A review. In: *The Parahippocampal Region*: *Implications for Neurological and Psychiatric Diseases*, 2nd edition. Scharfman HE, Witter, M. P., Schwarcz, R. (Eds.). New York, *The New York Academy of Sciences.*

Pitkänen, A., Savander, V., Ledoux, J. E. (1997). Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. *Trends Neurosci 20*: 517–523.

Quirk, G. J. (2002). Memory for Extinction of Conditioned Fear Is Long-lasting and Persists Following Spontaneous Recovery. *Learning Memory 9*: 402–407.

Quirk, G. J., Armony, J. L., Ledoux, J. E. (1995). Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron 15*: 1029–1039.

Quirk, G. J., Likhtik, E., Pelletier, J. G., Pare, D. (2003). Stimulation of Medial Prefrontal Cortex Decreases the Responsiveness of Central Amygdala Output Neurons. *J Neurosci 23*: 8800–8807.

Quirk, G. J., Russo, G. K., Barron, J. L., Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J Neurosci 20*: 6225–6231.

Rauch, S. L., Whalen, P. J., Shin, L. M., Mcinerney, S. C., Macklin, M. L., Lasko, N. B., Orr, S. P., Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry 47*: 769–776.

Rauch, S. L., Shin, L. M., Segal, E., Pitman, R. K., Carson, M. A., McMullin, K., *et al*. (2003). Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport 14*: 913–916.

Rescorla, R. A. (2001). Retraining of extinguished Pavlovian stimuli. *J Experi Psychology*: *Animal Behavior Processes 27*: 115–24.

Rogan, M. T., Staubli, U. V., Ledoux, J. E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature 390*: 604–607.

Rolls, E. T. (1999). *The Brain and Emotion*, New York, Oxford University Press.

Romanski, L. M., Ledoux, J. E. (1992). Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. *J Neurosci 12*: 4501–4509.

Rosenkranz, J. A., Grace, A. A. (2001). Dopamine Attenuates Prefrontal Cortical Suppression of Sensory Inputs to the Basolateral Amygdala of Rats. *J Neurosci 21*: 4090–4103.

Russchen, F. T. (1982). Amygdalopetal projections in the cat. I. Cortical afferent connections. A study with retrograde and anterograde tracing techniques. *J Comp Neurol 206*: 159–79.

Saddoris, M. P., Gallagher, M., Schoenbaum, G. (2005). Rapid Associative Encoding in Basolateral Amygdala Depends on Connections with Orbitofrontal Cortex. *Neuron 46*: 321–331.

Santini, E., Muller, R. U., Quirk, G. J. (2001). Consolidation of Extinction Learning Involves Transfer from NMDA-Independent to NMDA-Dependent Memory. *J Neurosci 21*: 9009–9017.

Sarter, M., Markowitsch, H. J. (1984). Collateral innervation of the medial and lateral prefrontal cortex by amygdaloid, thalamic, and brain-stem neurons. *J Comp Neurol. 224*: 445–60.

Schaefer, S. M., Jackson, D. C., Davidson, R. J., Aguirre, G. K., Kimberg, D. Y., Thompson-Schill, S. L. (2002). Modulation of amygdalar activity by the conscious regulation of negative emotion. *J Cognitive Neurosci 14*: 913–21.

Schoenbaum, G., Chiba, A. A., Gallagher, M. (1999). Neural encoding in orbitofrontal cortex and basolateral amygdala durnig olfactory discrimination learning. *J Neurosci 19*: 1876–1884.

Sesack, S. R., Deutch, A. Y., Roth, R. H., Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *J Comp Neurol 290*: 213–42.

Shi, C. J. & Cassell, M. D. (1998) Cascade projections from somatosensory cortex to the rat basolateral amygdala via the parietal insular cortex. *J Comp Neurol 399*: 469–491.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., *et al.* (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Archi Gen Psychiatry 61*: 168–176.

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., *et al.* (2001). An fMRI study of anterior cingulate cortex function in posttraumatic stress disorder. *Bioll Psychiatry 50*: 932–942.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., Mcmullin, K., Martis, B., Macklin, M. L., Lasko, N. B., Cavanagh, S. R., Krangel, T. S., Orr, S. P., Pitman, R. K., Whalen, P. J., Rauch, S. L. (2005). A Functional Magnetic Resonance Imaging Study of Amygdala and Medial Prefrontal Cortex Responses to Overtly Presented Fearful Faces in Posttraumatic Stress Disorder. *Arch Gen Psychiatry 62*: 273–281.

Smith, Y., Paré, J., Paré, D. (2000). Differential innervation of parvalbumin-immunoreactive interneurons of the basolateral amygdaloid complex by cortical and intrinsic inputs. *J Comp Neurol 416*: 496–508.

Sripanidkulchai, K., Sripanidkulchai, B., Wyss, J. M. (1984). The cortical projection of the basolateral amygdaloid nucleus in the rat: a retrograde fluorescent dye study. *J Comp Neurol 229*: 419–31.

Stefanacci, L., Amaral, D. G. (2002). Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol 451*: 301–23.

Swanson, L. W., Petrovitch, G. D. (1998). What is the amygdala? *Trends Neuroscis 21*: 323–330.

Takagishi, M., Chiba, T. (1991). Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. *Brain Res 566*: 26–39.

Tomkins, S. S., Mccarter, R. (1964). What and Where Are the Primary Affects? Some Evidence for a Theory. *Percep Motor Skills 18*: 119–58.

Van Hoesen, G. W., Morecraft, R. J., Vogt, B. A. (1993). Connections of the monkey cingulate cortex. In B.A., Vogt and M., Gabriel (Ed.) *Neurobiology of Cingulate Cortex and Limbic Thalamus*: *A Comprehensive Handbook* 249–267.

Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse 51*: 32–58.

Walker, D. L., Ressler, K. J., Lu, K. T, Davis, M. (2002). Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J Neurosci 22*: 2343–2351.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Curr Direc Psycholog Sci 7*: 177–188.

Whalen, P. J., Bush, G., Mcnally, R. J., Wilhelm, S., Mcinerney, S. C., Jenike, M. A., Rauch, S. L. (1998). The emotional counting stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry 44*: 1219–1228.

Whalen, P. J., Shin, L. M., Mcinerney, S. C., Fischer, H. (2001). A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion 1*: 70–83.