

# Resolving Emotional Conflict: A Role for the Rostral Anterior Cingulate Cortex in Modulating Activity in the Amygdala

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## Summary

Effective mental functioning requires that cognition be protected from emotional conflict due to interference by task-irrelevant emotionally salient stimuli. The neural mechanisms by which the brain detects and resolves emotional conflict are still largely unknown, however. Drawing on the classic Stroop conflict task, we developed a protocol that allowed us to dissociate the generation and monitoring of emotional conflict from its resolution. Using functional magnetic resonance imaging (fMRI), we find that activity in the amygdala and dorsomedial and dorsolateral prefrontal cortices reflects the amount of emotional conflict. By contrast, the resolution of emotional conflict is associated with activation of the rostral anterior cingulate cortex. Activation of the rostral cingulate is predicted by the amount of previous-trial conflict-related neural activity and is accompanied by a simultaneous and correlated reduction of amygdalar activity. These data suggest that emotional conflict is resolved through top-down inhibition of amygdalar activity by the rostral cingulate cortex.

## Introduction

As William James first pointed out (James, 1890), we are exposed, in our everyday life, to a larger number of sensory stimuli than we can dedicate processing resources to. As a result, we engage attentional mechanisms to prioritize processing and diminish distraction by stimuli irrelevant to the task at hand (Broadbent, 1958). To ensure optimal performance, the brain is thought to resolve “conflict” by monitoring continuously for distracters that produce responses that are incompatible with the current task (Botvinick et al., 2001). Emotionally salient stimuli, such as those that signal potential danger, are

particularly effective in interfering with ongoing cognitive processing (LeDoux, 2000; Mathews, 1990; Tipples and Sharma, 2000). However, despite the important role that control over the effects of emotional distracters plays in both normal functioning and in clinical mood and anxiety disorders (Mathews, 1990; Mathews and MacLeod, 1985), the neural mechanisms by which emotional conflict is monitored and resolved are largely unknown. This stands in sharp contrast to nonemotional (cognitive) conflict, where extensive knowledge already exists. Here, we exploit some of the methodological insights gained from the study of cognitive conflict resolution and apply them to emotional conflict.

## Assessing Emotional Conflict

The classic paradigm for studying nonemotional conflict is the color-word Stroop task (MacLeod, 1991; Stroop, 1935). In this task, subjects are asked to indicate the type-face (ink) color of a word (e.g., “green” or “red”) that is also the name of a color (e.g., “RED” or “GREEN”). When the ink color and the word meaning are not the same (i.e., incongruent), processing of the word meaning and the ink color lead to different, incompatible responses, thereby generating conflict and slowing reaction times. In the Stroop task, therefore, semantic incompatibility between the task-relevant and task-irrelevant stimulus dimensions produces response conflict.

Previous studies of emotional conflict employed a different form of the Stroop task, the “emotional Stroop” task. In this task, subjects are asked to identify the ink color of words that are either emotionally neutral (e.g., “apple”) or emotionally salient (e.g., “death”) (Mathews and MacLeod, 1985; McKenna, 1986). Slowing of reaction times for color naming of emotional words relative to neutral words serves as a measure of emotional interference. The emotional Stroop task, however, is not thought to assess directly the interference of emotional processing with cognitive processing. Rather it assesses the ability of emotional stimuli, processed in parallel, to withdraw attention from the main task. This is because the meaning of the emotional word stimuli is neither semantically related to the task-relevant information (ink color) nor does it lead to responses that directly compete with the selection of the correct response (Algom et al., 2004). The traditional emotional Stroop task, therefore, does not provide a measure of emotional conflict comparable to the measure of cognitive conflict provided by the classic color-word Stroop task. Moreover, in normal subjects, behavioral interference by these emotional distracters is either not detected at all (Williams et al., 1996) or habituates very rapidly (Compton et al., 2003; McKenna, 1986). Such lack of reliable behavioral effects limits the conclusions that can be drawn from previous imaging studies that used emotional Stroop-like tasks (Bishop et al., 2004; Compton et al., 2003; Whalen et al., 1998).

To assess more directly the effects of emotional conflict, we developed a paradigm in which emotional conflict arises from incompatibility between the task-relevant

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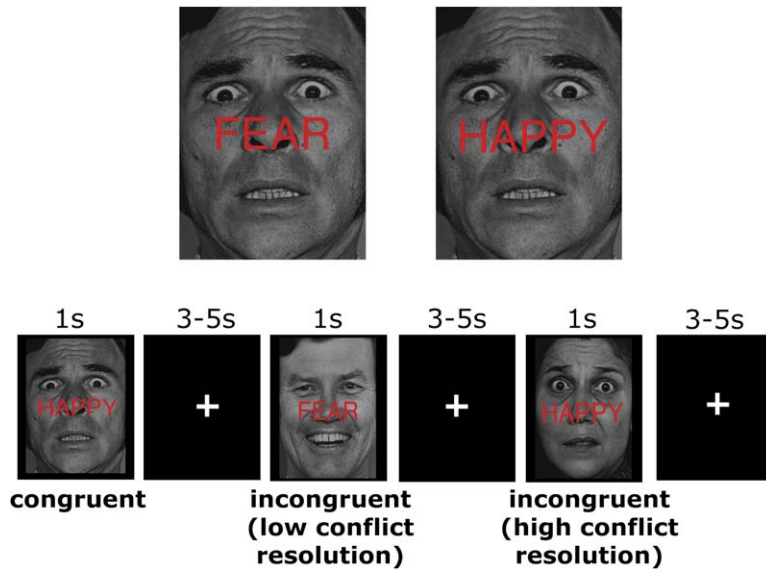


Figure 1. Stimuli and Example Timelines Used in the Emotional Conflict Task

Subjects were asked to identify the affect of faces with fearful or happy expressions that had either “fear” or “happy” written across them. Stimuli were either congruent or incongruent with respect to facial expression and word, which created emotional conflict.

and task-irrelevant emotional dimensions of a stimulus. We modified the classic color-word Stroop paradigm and developed an emotional conflict task in which faces with fearful and happy expressions were presented with the words “happy” or “fear” written across them (cf. Carroll and Young, 2005). We then asked subjects to identify the emotional expression of the faces while ignoring the words, which were either congruent or incongruent with the facial expression (see [Experimental Procedures](#) and [Figure 1](#) for example stimuli). Incongruent stimuli were thus associated with response conflict that arose from an emotional incompatibility between task-relevant and task-irrelevant stimulus dimensions (e.g., a fearful expression with the word “happy”). Our emotional conflict task therefore represents an appropriate emotional analog to the color-word Stroop task (Algom et al., 2004).

### The Neural Circuitry of Conflict Processing

The anterior cingulate cortex has frequently been thought to play a critical role in executive attention (Botvinick et al., 2004; Bush et al., 2000; Carter et al., 1999; Ridderinkhof et al., 2004). Examination of cytoarchitecture and connectivity patterns, as well as lesion and imaging studies, however, has led some authors to divide the anterior cingulate cortex into a dorsal “cognitive” division and a ventral “affective” division (Bush et al., 2000; Devinsky et al., 1995; Vogt et al., 1992). The dorsal cingulate and adjacent dorsomedial prefrontal cortex are connected with “cognitive” regions such as the lateral prefrontal and motor/premotor cortices (van Hoesen et al., 1993). The ventral division, composed of rostral (pregenual) and subgenual components, is connected with “affective” regions such as the amygdala (Carmichael and Price, 1995; van Hoesen et al., 1993). The dorsal and ventral divisions of the anterior cingulate are also interconnected with each other (Musil and Olson, 1988a, 1988b; van Hoesen et al., 1993).

Response conflict on cognitive tasks commonly activates the dorsal division of the anterior cingulate and adjacent dorsomedial prefrontal cortex (Botvinick et al., 2004; Bush et al., 2000; Ridderinkhof et al., 2004). It was uncertain, however, whether these regions were

responsible for monitoring or for resolving conflict, and thus resolution of this issue required an experimental paradigm capable of dissociating conflict monitoring from conflict resolution (Botvinick et al., 2001, 2004; Kerns et al., 2004; MacDonald et al., 2000; Posner and DiGirolamo, 1998; Posner et al., 1988). Such a dissociation can be achieved by examining the behavioral effects of trial sequence, and these studies reveal that there is less reaction time interference (i.e., less conflict) for incongruent trials if they are preceded by an incongruent trial than if they are preceded by a congruent trial (Botvinick et al., 1999; Egner and Hirsch, 2005a, 2005b; Gratton et al., 1992; Kerns et al., 2004). These findings suggest that the conflict generated by an immediately prior incongruent trial activates an anticipatory mechanism, which leads to improved conflict resolution on the next trial (Botvinick et al., 2001). Incongruent trials can thus be separated depending on whether they are associated with high conflict resolution and consequently less conflict (an incongruent trial preceded by an incongruent trial) or low conflict resolution and thus more conflict (an incongruent trial preceded by a congruent trial). Neural activity in regions responsible for either generating or monitoring conflict should reflect the amount of behavioral conflict, resulting in higher activity for low conflict resolution trials in these regions, while in brain regions implicated in conflict resolution, reduced conflict should be associated with increased neural activity.

This distinction between otherwise identical incongruent trials allows for a dissociation between conflict generating/monitoring and conflict resolving processes. Indeed, a series of recent neuroimaging studies have found activity in the dorsal cingulate and the dorsomedial prefrontal cortex associated with the monitoring of conflict, whereas activity in the lateral prefrontal cortices was associated with the resolution of conflict (Botvinick et al., 1999; Kerns et al., 2004; Egner and Hirsch 2005a). The dorsal cingulate most likely does not constitute a functionally homogenous region. The dorsal cingulate and adjacent dorsomedial prefrontal cortex, for example, have additional roles in general outcome evaluation

(Rushworth et al., 2004), volitional processes (Nachev et al., 2005), attentional selection (Posner and DiGirolamo, 1998; Weissman et al., 2004), and autonomic control (Critchley et al., 2003).

In contrast to the understanding we now have of cognitive conflict, emotional conflict has not been comparably investigated. A variety of tasks involving emotional processing in general (Bush et al., 2000), the processing of emotional distracters (Vuilleumier et al., 2001), and particularly the processing of negatively valenced stimuli in emotional Stroop tasks (Bishop et al., 2004; Whalen et al., 1998) all activate the rostral anterior cingulate, part of the ventral “affective” division. By extrapolation from the involvement of the dorsal cingulate in the processing of cognitive conflict, the rostral and subgenual cingulate have been thought to play a role in processing emotional conflict (Bishop et al., 2004; Bush et al., 2000; Whalen et al., 1998). These studies, however, presented emotional stimuli in blocks (Bishop et al., 2004; Bush et al., 2000; Compton et al., 2003; Whalen et al., 1998) and therefore could not distinguish the mechanisms associated with the monitoring of conflict from those associated with the resolution of conflict, as has been possible for cognitive conflict. The exact function of the rostral cingulate in emotional conflict, therefore, remains unclear. We wanted to determine whether the rostral cingulate acts as the emotional analog to the dorsal cingulate by monitoring emotional conflict, as has been suggested by some investigators (Bishop et al., 2004; Whalen et al., 1998), or whether it plays a different role, for instance by resolving emotional conflict.

In the current study, we distinguished between trials of high and low conflict resolution to differentiate the neural processes that track emotional conflict (because they are involved in conflict generation or monitoring) from those associated with emotional conflict resolution. We expected that the emotional nature of the stimuli will recruit regions such as the amygdala and rostral cingulate. We also reasoned that because emotional conflict in our task results in response conflict, regions involved in processing response conflict may also be activated.

After determining which regions tracked emotional conflict and which regions were involved in emotional conflict resolution, we turned our attention to their functional interconnectivity. We specifically tested whether neural conflict resolution would be recruited in a flexible manner on the current trial, to the degree appropriate for the amount of conflict signaled by conflict-tracking regions on the previous trial (Botvinick et al., 2001; Kerns et al., 2004). Finally, for conflict resolution to be successful, the regions underlying conflict resolution must in turn regulate the source of the emotional conflict. Thus, we examined whether increased activity in regions involved in conflict resolution was associated with decreased activity in upstream regions involved in conflict processing.

## Results

### Detection and Resolution of Emotional Conflict

We carried out the emotional conflict task on a group of 19 healthy volunteers and, based on reaction times, found robust behavioral interference associated with

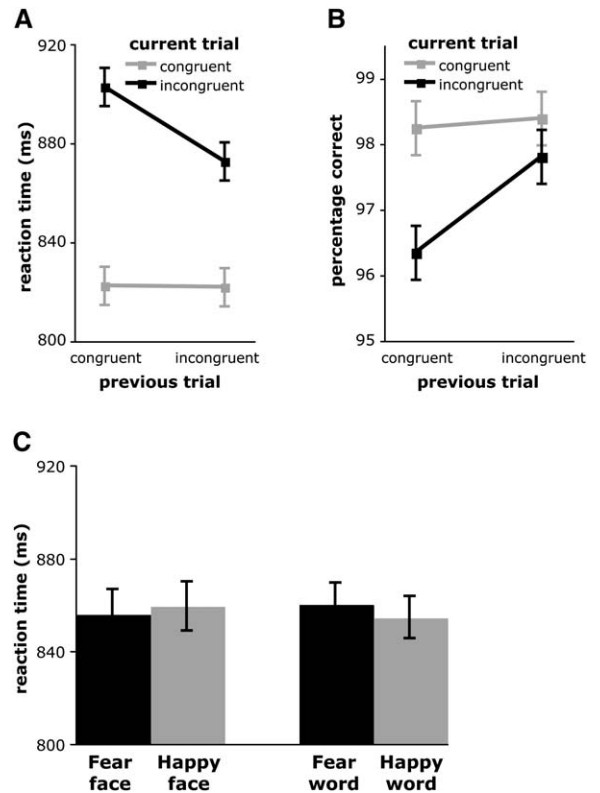


Figure 2. Behavioral Dissociation between Conflict Monitoring and Conflict Resolution

Mean reaction times (A) and accuracy (B)  $\pm$ SEM for incongruent and congruent trials split by previous-trial and current types. (C) Reaction times in this task are not driven by the emotional content of the faces or words independent of whether they were congruent or incongruent.

emotional conflict in every subject (all incongruent versus congruent trials,  $p = 0.0000002$ ; Figure 2A). A similar effect was seen for accuracy ( $p = 0.0001$ , Figure 2B), indicating that the reaction-time effect was not a result of a speed-accuracy tradeoff.

We next compared reaction times on low conflict resolution trials (incongruent trials that followed congruent ones) with high conflict resolution trials (incongruent trials that followed incongruent ones). The data showed reduced reaction time interference during high conflict resolution trials ( $p = 0.01$ , Figure 2A), consistent with activation of an anticipatory mechanism by the previous incongruent trial, which bolstered conflict resolution on the current trial (previous  $\times$  current trial ANOVA  $p = 0.03$ ; Figure 2A). A similar effect was evident at a trend level for accuracy ( $p = 0.096$ ; Figure 2B). Also, as seen in Figure 2C, no reaction time differences were seen between presentation of fearful and happy faces ( $p = 0.76$ ) or words ( $p = 0.54$ ), which were counterbalanced across congruency conditions, suggesting that behavior in this task was driven primarily by emotional conflict.

Finally, since high conflict resolution trials entailed a repetition of an incongruent stimulus, which does not occur on low conflict resolution trials, it remained a possibility that repetition priming rather than conflict resolution could mediate faster reaction times in high conflict resolution trials (Mayr et al., 2003). In designing the

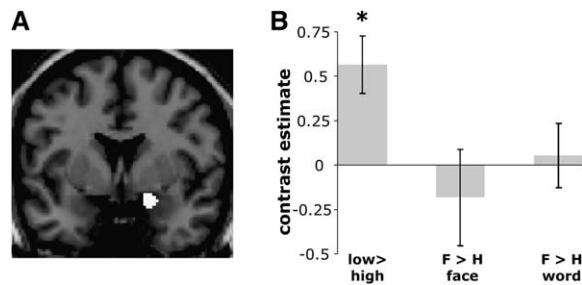
task we avoided direct stimulus repetition. However, we could not avoid repetition of the stimulus category in some high conflict resolution trials (e.g., fearful face and happy word followed by another fearful face and happy word). We therefore compared reaction times on high conflict resolution trials in which category repetition occurred to trials in which repetition did not occur (Egner and Hirsch, 2005a) and found no differences in reaction times ( $p = 0.45$ ).

Together, these data confirm that behavioral interference arising from emotional conflict can be detected in healthy volunteers and that conflict leads to enhancement of conflict resolution on the subsequent trial. We next used these behavioral findings to investigate differences in regional brain activity associated with emotional conflict monitoring and resolution using fMRI. Specifically, we focused on the distinction between high and low conflict resolution trials in order to dissociate conflict monitoring from conflict resolution (Botvinick et al., 1999; Egner and Hirsch, 2005a; Kerns et al., 2004).

#### Emotional Conflict Monitoring and Resolution Effects in the Amygdala and Prefrontal Cortex

An a priori region of interest analysis in the amygdalae (see *Experimental Procedures*) revealed a cluster in the right amygdala where activity was greater in low than high conflict resolution trials ([18, 2, -16],  $Z = 2.99$ ; *Figures 3A and 3B*), suggesting that activity in the amygdala reflects the amount of emotional conflict. No voxels in the amygdala were more active in high than low conflict resolution trials, event at a lenient  $p < 0.05$ , uncorrected. The effect of emotional conflict in the amygdala also did not differ between fearful and happy face targets, which were counterbalanced across low and high conflict resolution trials (all voxels  $p > 0.1$ , data not shown). In addition, no difference was observed in the region of the amygdala sensitive to emotional conflict for the response to fearful versus happy faces ( $p = 0.51$ ) or fear versus happy words ( $p = 0.76$ ; *Figure 3B*). This is consistent with previous studies that have shown comparable amygdala activations to fearful and happy facial expression (Fitzgerald et al., 2006; Yang et al., 2002). These results therefore show that emotional conflict itself leads to activation of the amygdala, independently of stimulus valence.

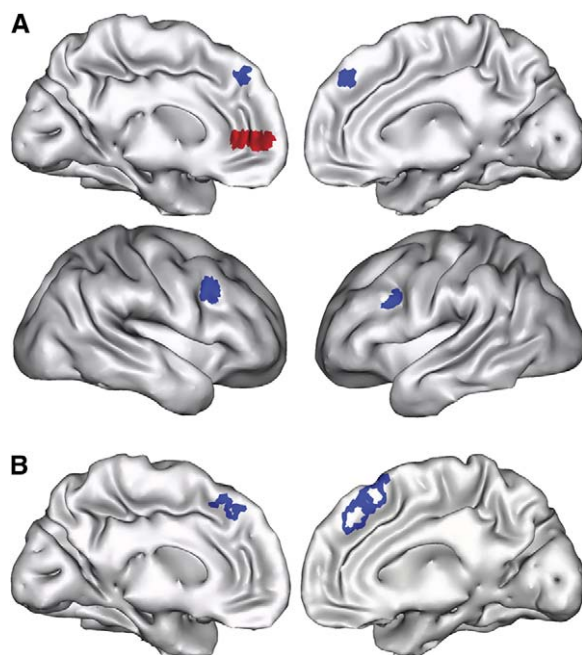
Next, we focused on the medial and lateral prefrontal cortices, including the anterior cingulate, as these frontal regions have been previously implicated in cognitive conflict monitoring and resolution (Botvinick et al., 1999, 2001, 2004; Egner and Hirsch, 2005b; Kerns et al., 2004; MacDonald et al., 2000; Ridderinkhof et al., 2004). Within the prefrontal cortex, activity tracking the amount of emotional conflict (low > high conflict resolution trials) was observed in three areas: midline dorsomedial prefrontal and bilateral dorsolateral prefrontal cortices (DMPFC [-2, 38, 38]  $Z = 4.08$ , right DLPFC [42, 14, 32]  $Z = 3.7$  and [44, 18, 52]  $Z = 3.13$ , left DLPFC [-44, 18, 24]  $Z = 3.63$ ; blue in *Figure 4A*). By contrast, activity corresponding to the resolution of conflict (high > low conflict resolution trials) was observed in only one area: the rostral anterior cingulate ([-10, 48, 0]  $Z = 4.02$  and [-10, 36, 2]  $Z = 3.47$ ; red in *Figure 4A*). These data suggest that the rostral cingulate is engaged during



**Figure 3. The Amygdala Is Involved in Conflict Processing**  
(A) Active right amygdala cluster in the low > high conflict resolution contrast (displayed at  $p < 0.005$ , uncorrected).  
(B) Mean right amygdala activity ( $\pm$ SEM) is greater in low than high conflict resolution trials. No significant differences were seen in response to emotional content independent of stimulus incongruency. Contrast estimates ( $\beta$  weights) correspond to an average of all suprathreshold voxels.

emotional conflict resolution and not for the monitoring or generation of such conflict.

Since high conflict resolution trials are associated with faster reaction times than low conflict resolution trials, greater rostral cingulate activity in high conflict resolution trials could in theory simply be a result of high conflict resolution trials being “easier.” This view is consistent with the involvement of the rostral cingulate in a “resting state” network, which may be suppressed during difficult tasks (Raichle et al., 2001). In our task,



**Figure 4. Cortical Regions Involved in Emotional Conflict Monitoring and Resolution**

(A) Frontal lobe regions whose activity is greater in high than low conflict resolution trials (red) or in low than high conflict resolution trials (blue), displayed at  $p < 0.001$ , uncorrected.  
(B) Conjunction between regions showing both greater activity in high than low conflict resolution trials and congruent than incongruent trials (red) or greater activity in low than high conflict resolution trials and incongruent than congruent trials (blue) at a lenient uncorrected threshold of  $p < 0.05$ .

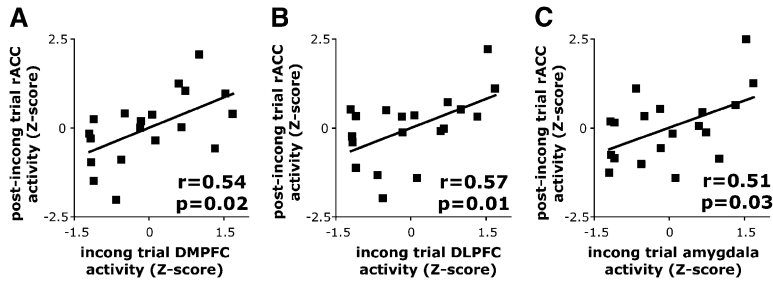


Figure 5. Recruitment of the Rostral Cingulate Is Predicted in an Anticipatory Fashion by Previous Trial Activity in Regions Tracking Conflict

The amount of conflict signal in the dorsomedial prefrontal cortex (A), dorsolateral prefrontal cortex (B), or amygdala (C) on incongruent trials correlates with activity in the rostral cingulate (rACC) on the following (i.e., postincongruent) trial. Regional activity was defined by the average of all suprathreshold voxels described in Figures 3 and 4. Activity in each region has been adjusted for shared variance with a fourth, task-responsive region outside the frontal lobe to control for nonspecific effects of individual differences in the magnitude of brain activation. Plotted are the postadjustment Z scores.

an even greater reaction time difference was observed between all congruent and all incongruent trials. The “trial ease” explanation would predict that rostral cingulate activity should be greater in high than low conflict resolution trials and also greater in congruent than incongruent trials. We therefore conducted a conjunction analysis for voxels activated at a very lenient threshold (uncorrected  $p < 0.05$ ) in both high > low conflict resolution trials and congruent > incongruent trials (Figure 4B). Even at this lenient threshold we found no significant voxels in the rostral cingulate, arguing that activity in the rostral cingulate does not merely reflect the ease of the trial but rather reflects an active process of conflict resolution. By contrast, as would be expected of a conflict-monitoring region, the dorsomedial and dorsolateral prefrontal cortices (Figure 4B and data not shown) were both more active in low than high conflict resolution trials and in incongruent than congruent trials.

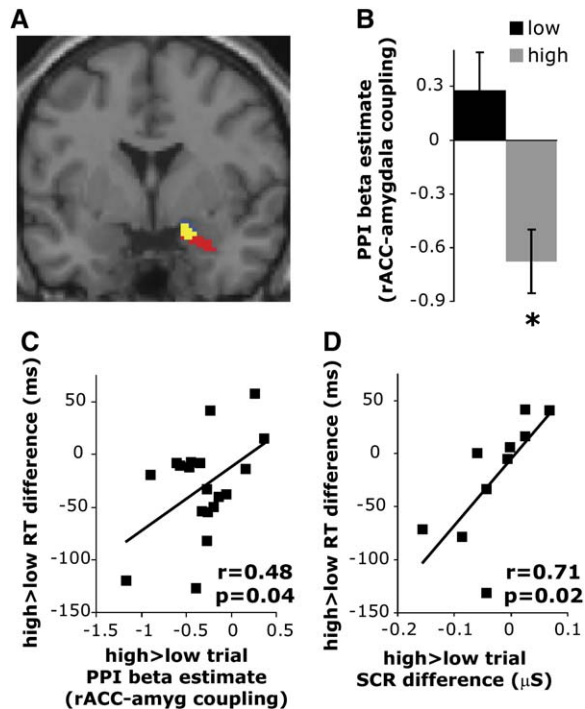
#### Sequential Emotional Conflict Tracking and Resolution Involve an Interaction between the Amygdala and the Rostral Cingulate

A critical prediction of a sequential conflict monitoring and resolution model is that the amount of previous-trial conflict determines the amount of conflict resolution on the current trial and, thus, that conflict resolution acts in an anticipatory fashion. We evaluated activity in regions tracking the amount of emotional conflict (amygdala and dorsomedial and dorsolateral prefrontal cortices) on incongruent trials and correlated it with rostral cingulate activity on the following trial (i.e., postincongruent trials). To control for nonspecific effects of general brain activity, we removed common correlations between our regions of interest and a control region, the left supramarginal gyrus, which was the most significant task-responsive region outside of the frontal lobe (cf. Kerns et al., 2004). We found that incongruent trial activity in the dorsomedial prefrontal cortex ( $r = 0.54$ ,  $p = 0.02$ ), the right dorsolateral prefrontal cortex ( $r = 0.57$ ,  $p = 0.01$ ), and the amygdala ( $r = 0.52$ ,  $p = 0.03$ ) all predicted rostral cingulate activity on the following trial (Figures 5A–5C). Correlations using the left dorsolateral cortex were nonsignificant ( $p > 0.2$ ). Performing the correlations without removing the variance shared with the left supramarginal gyrus did not change the results (data not shown).

How might activation of the rostral cingulate mediate the resolution of emotional conflict? One possibility is through an interaction with the amygdala, a region we have found to reflect the amount of emotional conflict. The rostral cingulate projects to the amygdala, and the amygdala in turn regulates various sites, including the hypothalamus and through it the sympathetic nervous system (Bechara et al., 1995; Paxinos, 1990). In experimental animals, inhibition of the amygdala by the medial prefrontal cortex (Quirk et al., 2003; Rosenkranz and Grace, 2002) is thought to be important for the extinction of learned fear (Delgado et al., 2006; Quirk et al., 2003). These data suggest that, in humans, increased activity in the rostral anterior cingulate may also lead to a reduction in the activity of the amygdala, which would thereby reduce emotional responsivity.

To examine interregional connectivity, we carried out a psychophysiological interaction (PPI) analysis (see Experimental Procedures), in which we examined the context-specific relationship between the activity in two regions during each trial type on an acquisition-by-acquisition basis (Friston et al., 1997). We found a significant inverse relationship between conflict resolution-related activity (high versus low conflict resolution trials) in the rostral cingulate and simultaneous activity in the right amygdala ([16, 0, –16]  $Z = 2.87$ ; left amygdala  $p > 0.1$ ). Shown in red in Figure 6A is the amygdala cluster negatively coupled to the rostral cingulate, while in blue is the right amygdala cluster activated by emotional conflict, previously presented in Figure 3A, with the overlap in yellow. Thus, the region of the amygdala that responds to emotional conflict overlaps substantially with the region negatively coupled to the rostral cingulate.

We next examined activity in this overlapping region to understand the relationship between the amygdala and the rostral cingulate on each trial type. As shown in Figure 6B, during high conflict resolution trials, greater activity in the rostral cingulate predicted reduced activity in the amygdala ( $p = 0.001$ ). By contrast, during low conflict resolution trials, activity in the rostral cingulate did not significantly predict activity in the amygdala ( $p = 0.2$ ). Finally, we explored whether regulation of activity in the amygdala may arise from a cortical site apart from the rostral cingulate. Previous work has suggested an inverse relationship between activation in the amygdala and activation in the dorsal cingulate



**Figure 6.** The rACC Is Negatively Coupled with the Amygdala, and the Strength of This Coupling and of the Blunting of Autonomic Responsivity Predicts Successful Conflict Resolution

(A) Overlay of the right amygdala cluster showing significant negative coupling with the rostral cingulate in high versus low conflict resolution trials (red,  $p < 0.005$ , uncorrected) and the right amygdala cluster activated by emotional conflict from Figure 3A (blue). Overlapping voxels are displayed in yellow.

(B) Psychophysiological interaction ( $\pm$ SEM) between the rACC and the amygdala separately during low and high conflict resolution trials.

(C) Greater rACC-predicted reduction in amygdalar activity in high versus low conflict resolution trials (more negative high minus low resolution trial PPI coefficients) is associated with better conflict resolution (more negative high minus low conflict resolution trial RT differences;  $r = 0.48$ ,  $p = 0.04$ ).

(D) Greater dampening of autonomic responsivity (more negative high minus low conflict resolution trial SCR differences) predicted better conflict resolution ( $r = 0.71$ ,  $p = 0.02$ ).

and dorsomedial prefrontal cortex (Drevets and Raichle, 1998; Hariri et al., 2003). We therefore carried out another psychophysiological interaction analysis using a dorsomedial prefrontal cortical seed region. However, no voxels within either the left or right amygdala showed coupling with the dorsomedial prefrontal cortex (all  $p$  values  $> 0.1$ ). These data support the idea that the rostral cingulate may resolve emotional conflict in part by decreasing engagement of the amygdala by incongruent emotional distracters.

To test this idea further, we correlated the magnitude of rostral cingulate-predicted reduction of amygdalar activity with the behavioral success of emotional conflict resolution. Those individuals whose rostral cingulate predicted greater amygdalar activity reduction (in the psychophysiological interaction) showed significantly greater conflict resolution as measured by high minus low conflict resolution trial reaction time differences ( $r = 0.48$ ,  $p = 0.04$ ; Figure 6C).

One important function of the amygdala is to recruit autonomic responses to emotionally salient stimuli by activation of the sympathetic nervous system through the amygdala's hypothalamic projections (Bechara et al., 1995; Paxinos, 1990). To test whether suppression of autonomic responsivity, like suppression of amygdalar activity, was related to the success of conflict resolution, we recorded skin conductance responses (SCR) from an additional group of ten subjects performing the emotional conflict resolution task outside of the scanner (see Experimental Procedures). We found that greater blunting of the SCR on high conflict resolution trials relative to low conflict resolution trials predicted better emotional conflict resolution ( $r = 0.71$ ,  $p = 0.02$ , see Figure 6D; reaction time previous  $\times$  current trial ANOVA  $p = 0.04$ ). These data further support the idea that the rostral cingulate resolves emotional conflict by suppressing amygdalar activity and output, which leads to a blunting of the sympathetic autonomic response to incongruent emotional distracters.

#### Effective Connectivity between the Rostral Cingulate and the Amygdala Is Modulated by Previous-Trial Incongruency

Since the analysis of functional connectivity above does not allow inference about the directionality of the relationship (Friston et al., 2003), we were interested in further characterizing the dynamic changes in the directional interactions between the rostral cingulate and the amygdala as a function of whether the previous trial was incongruent and thus signaled the need for greater conflict resolution on the current trial. To do so, we carried out a dynamic causal modeling analysis. Dynamic causal modeling can indicate the directionality of inter-regional interactions, within the context of a model composed of a priori-defined anatomical regions with predetermined connections (Friston et al., 2003; Penny et al., 2004). Effects are divided into "intrinsic" connectivity in the absence of stimulation and modulatory effects associated with a particular experimental manipulation, such as the presence of previous-trial incongruency.

In dynamic causal modeling, a significant positive modulatory effect implies directional "activation" of the target by the source region, while a significant negative modulation implies "inhibition" of the target by the source region (see equation describing these effects in the Experimental Procedures section). Because of the spatial resolution of fMRI, these modulatory effects cannot be directly interpreted as excitatory or inhibitory effects at the cellular level, but rather describe how regions interact with each other as a whole in the context of pre-specified anatomical connectivity (Friston et al., 2003).

We tested a simple dynamic causal model focused on the interactions between the rostral cingulate and the amygdala. Input corresponding to all visual stimuli was allowed to drive both the rostral cingulate and amygdala, as intracerebral recordings in both regions in humans reveal similar, fast-latency responses to visual stimulation that can distinguish between aversive and nonaversive images (Kawasaki et al., 2001, 2005; Krolak-Salmon et al., 2004; Oya et al., 2002). Current-trial incongruency was also allowed to modulate the amygdala to rostral cingulate pathway (i.e., "forward" pathway). Previous-trial incongruency, a signal that leads to

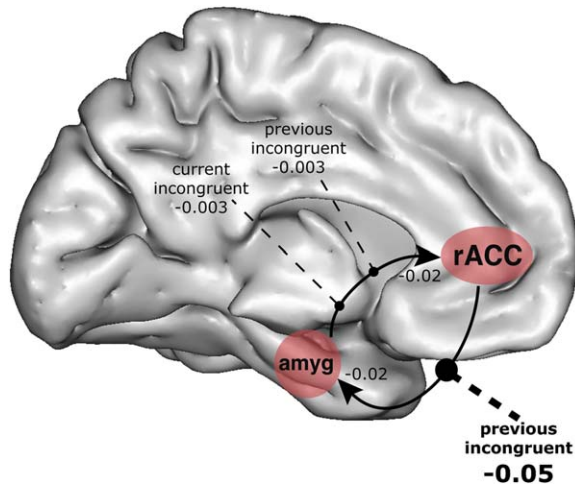


Figure 7. Previous-Trial Incongruency Increases Negative Effective Connectivity from the Rostral Cingulate to the Amygdala

Coupling coefficients for directional intrinsic connectivity are shown as values next to the arrows between the rACC and the amygdala, while coefficients for the modulatory (bilinear) effects are shown as values associated with additional lines intersecting with the intrinsic paths. The only significant effect in the model was greater negative modulation of the rACC to amygdala path by previous-trial incongruency, which triggers greater current-trial conflict resolution ( $p = 0.02$ ).

increased current-trial conflict resolution, was allowed to modulate the “forward” and “backward” pathways between the rostral cingulate and the amygdala.

We found that the intrinsic connections between the rostral cingulate and the amygdala were not significant at baseline ( $p > 0.68$  for both; Figure 7). Crucially, however, previous-trial incongruency led to a significant “inhibitory” modulation in the activation of the backward pathway from the rostral cingulate to the amygdala ( $p = 0.02$ ). Modulation of the amygdala to rostral cingulate pathway was not significant for either current- or previous-trial incongruency ( $p > 0.74$  for both). Furthermore, previous-trial incongruency modulated the backward connection more robustly than the forward connection ( $p < 0.05$ ). These results suggest that the triggering of increased current-trial conflict resolution by previous-trial incongruency is associated with a specific enhancement of a top-down inhibitory pathway from the rostral cingulate to the amygdala. These results are consistent with previous animal studies of medial prefrontal-amygdalar interactions (Delgado et al., 2006; Quirk et al., 2003; Rosenkranz and Grace, 2002).

## Discussion

We here report an approach for analyzing the neural mechanisms involved in the monitoring and resolution of emotional conflict. We find that response conflict arising from emotional incongruence leads to robust behavioral interference in healthy subjects and that this interference can be reduced through an anticipatory conflict-resolution mechanism that is recruited in response to conflict on the current trial. Activity in the amygdala and dorsomedial and dorsolateral prefrontal cortices

tracked the amount of emotional conflict created by emotionally incompatible stimuli, while activity in the rostral anterior cingulate cortex was associated with the resolution of this conflict. We also observed that activity in the amygdala and dorsomedial and dorsolateral prefrontal cortices on conflict trials directly predicted resolution-related activity in the rostral cingulate on the following trial, consistent with the sequential, anticipatory nature of conflict monitoring and resolution processes. Furthermore, we found that activation of the rostral cingulate during high conflict resolution trials was accompanied by a concomitant reduction in amygdalar activity. The degree to which rostral cingulate activation predicted reduced amygdalar activity, as well as the reduction in autonomic responsiveness, a function regulated by the amygdala, was related to subjects’ behavioral success at emotional conflict resolution. By analyzing effective connectivity between the amygdala and rostral cingulate we found that previous-trial incongruency, which leads to greater current-trial conflict resolution, was associated specifically with activation of an “inhibitory” top-down pathway from the rostral cingulate to the amygdala. These findings advance our understanding of the mechanisms by which amygdala activity is regulated for the purpose of resolving emotional conflict and, in particular, the function of the rostral cingulate during emotional conflict.

## Generation of Emotional Conflict by the Amygdala

In our task, unintended processing of the distracter word and its emotional significance in an incongruent stimulus led to activation of an emotional representation incompatible with that of the intended face target. Activation of incompatible emotional representations leads to a competition for some of the same neural resources in the processing of the face and word. This conflict for processing resources is represented in the brain both as emotional conflict and consequently as response conflict. Our data indicate that activity tracking the amount of conflict (either because regions generate or monitor conflict) can be seen in the amygdala and dorsomedial and dorsolateral prefrontal cortices. Because the amygdala is associated with affective processes and the dorsomedial and dorsolateral prefrontal cortices have been associated with nonemotional attentional processes, it is tempting to suggest that emotional conflict is generated in the amygdala, while the resultant response conflict involves the dorsomedial and dorsolateral prefrontal cortices, a hypothesis that can be tested in future work.

The role of the amygdala in the generation of emotional conflict is also supported by the fact that the amygdala is sensitive to both emotionally valenced words (Isenberg et al., 1999) and facial expressions (Breiter et al., 1996; Fitzgerald et al., 2006; Pessoa et al., 2003), indicating that both task processes (facial affect identification) and the task-irrelevant word distracters engage the amygdala. Moreover, previous studies have also found that the amygdala is particularly sensitive to ambiguity (a type of conflict), both in the context of interpreting facial expressions (Kim et al., 2003, 2004) and in the context of uncertainty during decision making (Hsu et al., 2005).

### Emotional Conflict Resolution through Top-Down Control of the Amygdala by the Rostral Cingulate

The amygdala regulation model described above posits further that the rostral cingulate is not the emotional analog to the dorsal cingulate (Bishop et al., 2004; Whalen et al., 1998), but rather is associated with the resolution of emotional conflict. Indeed, these results are consistent with a recent study tying rostral/subgenual cingulate activation to fear extinction (Phelps et al., 2004), a process that may be similar to emotional conflict resolution. Rostral cingulate activation has also been observed during placebo anxiety reduction, a process in which control over an emotional stimulus (an aversive picture) is recruited to diminish the effect of the emotional stimulus (Petrovic et al., 2005).

The top-down directionality of the rostral cingulate-amygdala interaction that we propose is supported by an extensive animal literature on the ability of the medial prefrontal cortex to inhibit the amygdala (Delgado et al., 2006; Quirk et al., 2003; Rosenkranz and Grace, 2002). However, one must also consider an alternative “bottom-up” model, in which the amygdala can be thought to normally exert an inhibitory effect on the medial prefrontal cortex, as has been suggested on the basis of fear-conditioning data in rodents (Garcia et al., 1999). Were the amygdala to habituate specifically during high conflict resolution trials (due to the repetition of incongruent stimuli not seen in low conflict resolution trials), decreased amygdalar activity would lead to decreased rostral cingulate inhibition, and as a consequence the rostral cingulate would be “disinhibited,” thus appearing to be activated. Therefore, with respect to the amygdala and rostral cingulate, the bottom-up model may equally well explain the differences in activity in these regions between high and low conflict resolution as a “top-down” model wherein the rostral cingulate inhibits the amygdala.

An important argument against the bottom-up model stems from the condition-specific psychophysiological interaction data. Specifically, were the rostral cingulate to inhibit the amygdala only when it is activated during the high conflict resolution trials (i.e., a top-down model), then negative coupling between the rostral cingulate and the amygdala would only be seen during these high conflict resolution trials, as we observed (Figure 6B). The bottom-up model, by contrast, would predict greater negative coupling in low compared to high conflict resolution trials. This is because amygdala inhibition of the rostral cingulate would likely be greatest when amygdala activation is greatest (i.e., during low conflict resolution trials). The bottom-up model is therefore inconsistent with our findings (Figure 6B).

To further strengthen a top-down inhibitory model of rostral cingulate function in regulating the amygdalar response to emotional conflict, we sought confirmatory evidence by examining effective connectivity between these two regions using dynamic causal modeling. We found that previous-trial incongruency, which triggers greater current-trial conflict resolution, led to specific strengthening of a pathway from the rostral cingulate to the amygdala. Moreover, this pathway was inhibitory, as increases in rostral cingulate activity were associated with decreased amygdalar activity in a direction-specific manner, supporting the top-down model. Our results are

also in line with a considerable amount of animal work, which has found that direct stimulation of the rodent medial prefrontal cortex leads to inhibition of both spontaneous and evoked activity in the amygdala (Quirk et al., 2003; Rosenkranz and Grace, 2002).

### A Neural Circuit for the Monitoring and Resolution of Emotional Conflict

In contrast to the conflict resolution function of the rostral cingulate, we found that emotional conflict monitoring was instead associated with a dorsomedial prefrontal region. Thus, we suggest that the dorsal cingulate/dorsomedial prefrontal cortex may have a conserved role in response conflict monitoring, regardless of whether the source of response conflict is cognitive or emotional. These data argue against a strict functional division of the cingulate/dorsomedial prefrontal cortex into a ventral affective and a dorsal cognitive component (Bush et al., 2000).

Interestingly, we find robust activity tracking the amount of conflict bilaterally in the dorsolateral prefrontal cortex. These data seem to differ qualitatively from studies of cognitive conflict, which have shown dorsolateral prefrontal cortical activity to be associated with conflict resolution, rather than monitoring (Egner and Hirsch, 2005a, 2005b; Kerns et al., 2004; MacDonald et al., 2000). However, recent meta-analyses report that the dorsolateral prefrontal cortex is activated by effortful attentional processing associated with incongruent stimuli in the Stroop task, task-switching, and high working memory loads (Derrfuss et al., 2005; Duncan and Owen, 2000; Wager et al., 2004). Therefore, the dorsolateral prefrontal activations associated with conflict in the current study may simply reflect generic effects of task difficulty. Whether lateral frontal regions display dissociable effects in cognitive versus emotional conflict processing can be addressed in future work. In addition, it will be important to explore how the rostral cingulate-mediated emotional regulation mechanism described here relates to the dorsolateral prefrontal-mediated emotion reappraisal mechanism described by others (Ochsner and Gross, 2005).

Finally, we have previously reported that individual differences in trait anxiety predicted reaction times and activation of the amygdala only when fearful faces were processed unconsciously, not when they were processed consciously (Etkin et al., 2004). This suggested that the unconscious biases in activation of the amygdala may be subject to secondary regulation by conscious processes (Etkin et al., 2004). Here we provide initial evidence that the rostral cingulate may be a key regulator of amygdalar activity and autonomic responsiveness and that this regulation is related to the behavioral success of emotional conflict resolution. Taken together, these studies suggest that the response to threat in healthy subjects involves two distinct stages—an initial unconscious, anxiety-related bias reflected in amygdala activation (and with it enhanced vigilance), followed by a secondary context-responsive suppression of amygdalar responsiveness by the rostral cingulate.

### Relevance to Mood and Anxiety Disorders

Our experiments on healthy subjects were carried out in order to understand what role the rostral cingulate



normally plays in nonpathological emotional conflict. But the data also allow us to better understand a variety of psychiatric disorders in which patients experience exaggerated interference from emotional distracters (Williams et al., 1996). Patients with post-traumatic stress disorder (PTSD), for example, consistently show a hypoactive rostral cingulate during trauma recall (Hull, 2002) and in tasks involving emotional processing or distraction. In PTSD, the severity of the symptoms also correlates with the degree of rostral cingulate hypoactivation (Shin et al., 2005). In depression, resistance to treatment is associated with hypoactivity of the rostral cingulate (Kumari et al., 2003). Indeed, lower rostral cingulate activity prior to treatment actually predicts a poor response to antidepressant therapy (reviewed in Etkin et al., 2005). As would be predicted by our results, in both depression and PTSD, hyperactivation of the amygdala occurs to both conscious and unconscious threat (Davidson et al., 2002; Hull, 2002; Rauch et al., 2000; Sheline et al., 2001). Taken together, these findings suggest that elevated amygdalar activity and exaggerated behavioral interference may be due to deficient amygdalar inhibition by the rostral cingulate, which leads to an inability to deal with emotional conflict. The capacity for recruitment of the rostral cingulate may thus determine how well an individual can cope with the intrusion of negative emotional stimuli or mental content.

## Experimental Procedures

### Subjects

Nineteen healthy volunteers (ten females, nine males; average age 26.6 [SD 5.2]) took part in the fMRI study, and ten healthy volunteers (three females, seven males; average age 25.1 [SD 7.2]) took part in the skin conductance study, all after giving their informed consent according to institutional guidelines for protection of human subjects (Columbia University).

### Experimental Paradigms

**Emotional conflict resolution task:** Stimuli were presented with Presentation software (Neurobehavioral Systems, <http://nbs.neuro-bs.com>) and during fMRI scanning were displayed on VisuaStim XGA LCD screen goggles (Resonance Technology, Northridge, CA). The task consisted of 148 presentations of happy or fearful facial expression photographs drawn from the set of Ekman and Friesen (Ekman and Friesen, 1976). Faces were cropped and the words "FEAR" or "HAPPY" written in prominent red letters across the face, such that word and expression were either congruent or incongruent (Figure 1A). Stimuli were presented for 1000 ms, with a varying inter-stimulus interval (ISI) of 3000–5000 ms (mean ISI = 4000 ms) during which a central fixation cross was shown. Stimuli were presented in pseudorandom order (counterbalanced for equal numbers of congruent-congruent, congruent-incongruent, incongruent-congruent, and incongruent-incongruent stimulus pairings). There were neither direct repetitions of the same face with varying word distracters, in order to avoid negative priming effects, nor direct repetitions of exact face-word-distracter combinations, in order to avoid repetition priming effects (Mayr et al., 2003). Genders, identities, and affects on the faces were randomized throughout the task, and stimulus occurrences were counterbalanced across trial types and response buttons. Subjects were instructed to respond as fast and accurately as possible, by pushing response buttons corresponding to "fear" (right index finger) or "happy" (right middle finger) for the affect expressed on the face. Behavioral data were analyzed in SPSS and consisted of reaction times (excluding error and post-error trials) and accuracy rate. For the skin conductance experiment, which took place outside of the scanner, this paradigm was adapted in order to distinguish individual skin conductance responses by using

an ISI of 14000–16000 ms (mean ISI = 15000 ms) and 111 presentations of happy or fearful expression faces. Stimuli were displayed on a 16 inch monitor, with the subjects sitting at a distance of ~20 inches and responding by pushing standard keyboard buttons.

### fMRI Data Acquisition

Functional data were acquired on a 1.5 Tesla GE Signa MRI scanner, using a gradient-echo, T2\*-weighted echoplanar imaging (EPI) with blood oxygen level-dependent (BOLD) contrast pulse sequence. Twenty-four contiguous axial slices were acquired along the AC-PC plane, with a 64 × 64 matrix and 19 cm field of view (voxel size 3 × 3 × 4.5 mm). A total of 397 volumes were acquired (TR = 2000, TE = 40, flip angle = 60). Structural data were acquired using a 3D T1-weighted spoiled gradient recalled (SPGR) pulse sequence with isomorphic voxels (1.5 × 1.5 × 1.5 mm) in a 24 cm field of view (256 × 256 matrix, 124 slices, TR 34 ms, TE 3 ms).

### SCR Data Acquisition

Skin conductance responses were acquired via silver electrodes (0.5 V DC excitation) attached to the palmar surfaces of the left index and middle finger. Signal was amplified and low-pass filtered (10 Hz cut-off) via a SA Bioamp amplifier (James Long Company, Caroga Lake, NY). Filtered analog SCR data were then digitized and stored at a sampling rate of 100 Hz, using Powerlab Chart 5 software (version 5.02, ADInstruments, Colorado Springs, CO).

### fMRI Data Analysis

All images were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; see <http://www.fil.ion.ucl.ac.uk/spm/spm2.html>) implemented in Matlab 6.5 (Mathworks, Inc., Natick, MA). The first five volumes were excluded from the analysis to allow for signal stability following onset transients. Data were corrected for differences in slice timing. Images were motion corrected, coregistered with subjects' SPGR scans, normalized to the MNI template space, resampled at 2 × 2 × 2 mm, and smoothed with a Gaussian kernel of 8 mm<sup>3</sup> FWHM (Friston et al., 1995a). A 128 s temporal high-pass filter was applied to the data to remove low-frequency noise. Regressors for the stimulus events (convolved with a canonical HRF) were created for congruent-congruent, congruent-incongruent, incongruent-congruent, and incongruent-incongruent trial types, with error and post-error trials modeled separately. We also included a regressor-of-no-interest reflecting the mean whole-brain activity on an acquisition-by-acquisition basis. This model was applied to normalized data across subjects in a generalized linear model approach (Friston et al., 1995b) and submitted to random-effects analyses using one-sample t tests.

Our amygdala search volume was defined by a bilateral amygdala mask using the AAL parameters available in the WFU PickAtlas (Maldjian et al., 2003), with a 3D dilation factor of 1 to ensure that we captured the entire amygdala. Group-level contrasts were thresholded within the amygdala at  $p = 0.005$  (uncorrected) and a ten voxel spatial extent, which yielded an equivalent correction for multiple comparisons and enriched for larger activation clusters (Forman et al., 1995). Our frontal cortical search volume was defined by a bilateral medial and lateral frontal gray matter mask using the WFU PickAtlas. We searched for significant voxels that met both the  $p = 0.005$  threshold and a more stringent  $p = 0.001$  threshold, also with a ten voxel spatial extent. As has been the custom in previous research (Phelps et al., 2004), we employed a more stringent threshold in the cortex than in the amygdalae, as cortical activations are known to be relatively easier to detect than amygdalar activations. Reported voxels correspond to standardized Montreal Neurological Institute (MNI) coordinate space. For the displayed section, the right side of the subject is the right side of the image.

For the psychophysiological interaction (PPI) analyses (Friston et al., 1997), we extracted the deconvolved time course from a 5 mm radius sphere around the group peak activation voxel for the rostral cingulate [−10, 48, 0]. Dorsomedial prefrontal activity was similarly extracted from a 5 mm radius sphere around its group peak voxel [−2, 38, 38]. Activity within the amygdala mask was then regressed on a voxel-wise basis against the product of this time course and the vector of the psychological variable of interest, with the physiological and the psychological variables serving as regressors of no interest. The results were then taken to

a random-effects group analysis using one-sample *t* tests. This analysis was repeated for the high and low conflict resolution trials alone, using amygdala activity extracted from the cluster showing both negative coupling with the rostral cingulate and greater conflict-related activity (i.e., yellow cluster in Figure 6A) and was performed using an ordinary least-squares algorithm implemented in Matlab.

Effective connectivity analyses were implemented using the dynamic causal modeling tool in SPM2 (Friston et al., 2003). Predictions about the observed data consist of a model with combined intrinsic connectivity in the absence of experimental manipulation and bilinear modulation, which reflects the effects of experimental variables. These effects were modeled by the following simplified equation (Friston et al., 2003):

$$dz_1/dt = (A + u_m B)z_2 + Cu_1$$

in which  $dz_1/dt$  is the state vector per unit time for the target region and  $z_2$  corresponds to time series data from the source region.  $u_1$  indicates the direct input to the model (i.e., all correct trials), while  $u_m$  indicates input from the modulatory variable onto intrinsic pathways specified by the model. Activity in the target region is therefore determined by an additive effect of the intrinsic connectivity with the source region ( $Az_2$ ), the bilinear variable ( $u_m Bz_2$ , corresponding to the modulatory experimental manipulation), and the effects of direct input into the model ( $Cu_1$ ).

Time series data were extracted from a 6 mm diameter sphere around each individual's peak voxel within the rostral cingulate (high > low conflict resolution) and right amygdala (low > high conflict resolution). Search volumes for these contrasts were the rostral cingulate cluster defined in the group contrast and the AAL-defined amygdala mask. Models were evaluated separately for each subject, and effective connectivity parameters were subjected to one-sample and two-sample *t* tests at the group level to determine significance.

#### SCR Data Analysis

Analysis was done in Matlab. The data were downsampled to 10 Hz, a derivative of the time course was calculated, and local maxima and minima were identified. We analyzed the magnitude of the SCR (max-min) for all events if they began within 4 s of the stimulus onset, were not associated with error and post-error trials, and were >0.02  $\mu$ S. SCR magnitudes were then subjected to ANOVA and regression analyses in SPSS.

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