

# Contextual Modulation of Amygdala Responsivity to Surprised Faces

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## Abstract

■ We recently demonstrated a functional relationship between fMRI responses within the amygdala and the medial prefrontal cortex based upon whether subjects interpreted surprised facial expressions positively or negatively. In the present fMRI study, we sought to assess amygdala–medial prefrontal cortex responsivity when the interpretations of surprised faces were determined by contextual experimental stimuli, rather than subjective judgment. Subjects passively viewed individual presentations of surprised faces preceded by either a negatively or positively valenced contextual sentence (e.g., She just found \$500 vs. She just lost \$500). Negative and positive sentences were carefully matched in

terms of length, situations described, and arousal level. Negatively cued surprised faces produced greater ventral amygdala activation compared to positively cued surprised faces. Responses to negative versus positive sentences were greater within the ventrolateral prefrontal cortex, whereas responses to positive versus negative sentences were greater within the ventromedial prefrontal cortex. The present study demonstrates that amygdala response to surprised facial expressions can be modulated by negatively versus positively valenced verbal contextual information. Connectivity analyses identified candidate cortical–subcortical systems subserving this modulation. ■

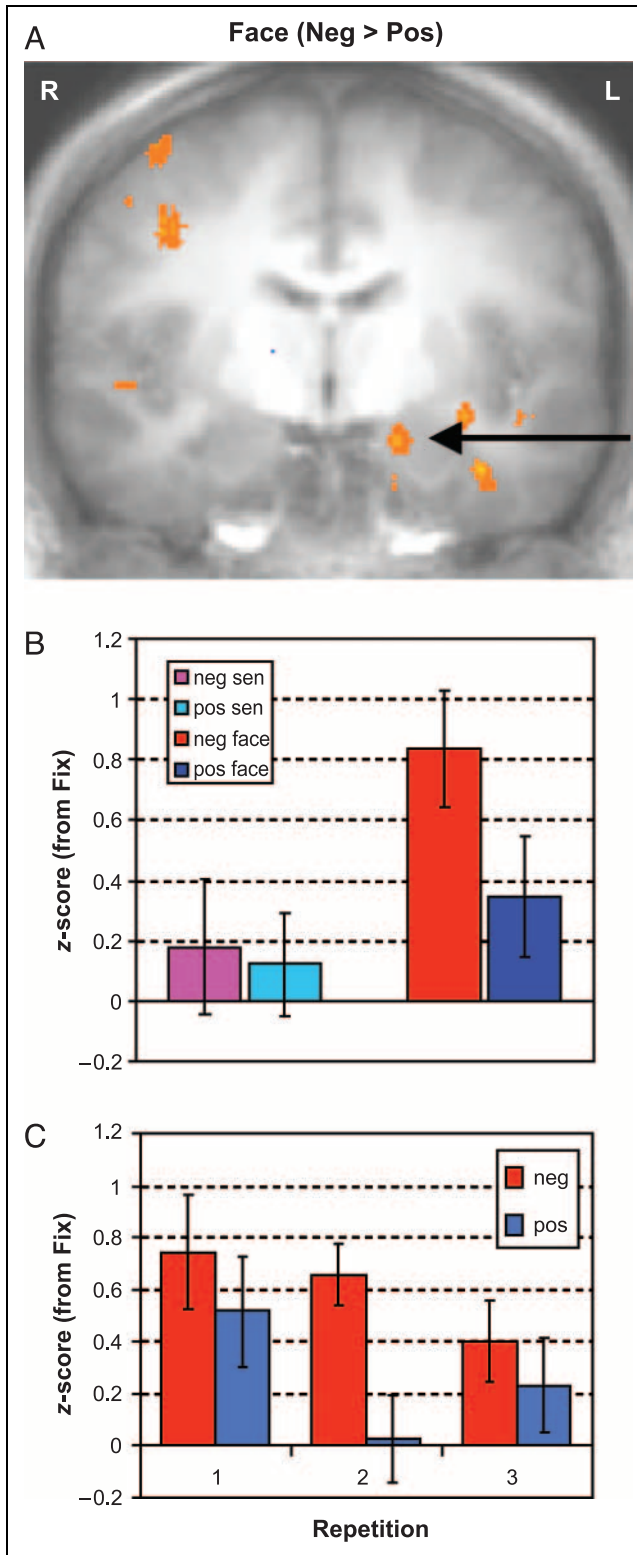
## INTRODUCTION

Several fMRI studies have demonstrated human amygdala responses to facial expressions of emotion, with a particular focus on fearful facial expressions (Whalen, Shin, et al., 2001; Phillips, Young, Scott, et al., 1998; Whalen, Rauch, et al., 1998; Phillips, Young, Senior, et al., 1997; Breiter et al., 1996; Morris, Frith, et al., 1996). One strategy to better understand the meaning or function of amygdala response to fearful faces is to examine its response to other expressions (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Whalen, Shin, et al., 2001; Phillips, Young, Senior, et al., 1997). Surprised expressions provide an important comparison expression for fear. For example, both expressions share the feature of eye widening consistent with the detection of an important eliciting event. Indeed, subjects who accurately label fearful expressions presented for >34 msec, label these expressions as “surprised” if presented for <34 msec (Ogawa & Suzuki, 1999), consistent with the notion that a basic significance signal is shared by these expressions (i.e., larger eye-whites). Eye widening observed in a conspecific is evidence of their increased vigilance, and a suggestion to the observer that they would do well to adopt a similar state (Whalen, 1998).

Animal and human studies support the possibility that the amygdala may be involved in the processes of both surprise and fear. For example, a bilateral amygdala lesion patient shows deficits in processing both the expressions of fear and surprise (see Adolphs, Tranel, Damasio, & Damasio, 1994: Figure 1). Stimulation of the amygdala produces eye widening in both animal (Applegate, Kapp, Underwood, & McNall, 1983; Kaada, 1972) and human subjects (see Gloor, 1997) and eye widening is observed in animal subjects during “early” aversive Pavlovian training trials (Masur, Dienst, & O’Neil, 1974). Related to these points, short-duration electrical stimulation of the human amygdala produces more subtle surprise reactions, whereas longer-duration stimulation is necessary for these same subjects to describe events associated with the feeling of fear (Gloor, 1997). Thus, the process of “surprise” represents an initial stage of information acquisition, and may be analogous to vigilance-related associative processes that can be shown to depend upon systems that include nuclei within the amygdaloid complex (e.g., central nucleus; see Holland, Chik, & Zhang, 2001; Whalen, 1998; Gallagher & Holland, 1994; Kapp, Whalen, Supple, & Pascoe, 1992).

Consistent with this line of reasoning, we recently demonstrated that the human amygdala is indeed responsive to surprised facial expressions (Kim et al., 2003). In this study, subjects showed individual differences in their judgments of surprised expressions (i.e.,

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**Figure 1.** (A) A statistical map presented in the coronal plane showing significant signal increases in the left amygdala (arrow) for the contrast of negatively versus positively cued surprised faces. (B) Bar graph depicting the magnitude of this effect (as a change from null fixation trials) as well as the responses at this locus to the sentence stimuli. (C) Bar graphs parsing this main effect by the three repeated presentations of each stimulus (average) within scan. R = right, L = left. Images thresholded at  $p < .01$ .

some offered positive ratings whereas others offered negative ratings). Despite these individual differences in valence judgments, we observed that more dorsal and medial portions of the right amygdala showed homogeneous signal increases across subjects, which we interpreted as consistent with responsivity to the information value of these stimuli regardless of their judged valence (i.e., something has occurred in your environment and you would do well to figure out what it is). We also observed parallel responsivity within a region of the right ventral and lateral amygdala where signal changes were significantly correlated with individual valence judgments (i.e., greater signal increases in subjects with more negative valence judgments).

Because reciprocal connections between the amygdala and the prefrontal cortex (PFC) subserve the assessment of outcomes predicted by valenced biologically relevant stimuli (Baxter & Murray, 2002; Quirk, Russo, Barron, & Lebron, 2000; Rolls, 1999; Schoenbaum, Chiba, & Gallagher, 1999; Damasio, 1994; Morgan, Romanowski, & LeDoux, 1993), in this same study, we assessed functional connectivity between the PFC and the right ventral amygdala locus sensitive to valence judgments, as a potential source of this variability. Specifically, amygdala and dorsomedial prefrontal cortex (dmPFC) responsivity was higher in subjects with more negative interpretations of surprised expressions, whereas ventromedial prefrontal cortex (vmPFC) responsivity was higher in subjects with more positive interpretations of these expressions. Accordingly, signal intensities within the amygdala were positively correlated with dmPFC responses, and inversely related to vmPFC responses. As this was a between-subject effect, an open question remained whether greater amygdala response to negative versus positive surprise could be demonstrated within subject.

The aim of the present study was to assess amygdala-PFC interaction in response to surprised faces when subjects were provided with additional contextual information that “disambiguated” the negative or positive context eliciting the surprised expression. To this end, in an event-related design, we preceded each surprised face presentation with a sentence that described either a positive or negative context for the ensuing facial expression (e.g., She just found \$500; She just lost \$500). Such a study design allowed us to (a) assess within-subject responsivity to positively versus negatively cued surprised expression presentations, (b) assess a valence manipulation while holding the features constant between differentially valenced face presentations, and (c) separately model amygdala fMRI responses to faces from those to the contextual sentences. We predicted that the amygdala would be more responsive to negatively versus positively cued surprised faces. Based upon our previous findings (Kim et al., 2003), and anatomical data demonstrating amygdala-PFC connectivity (see Discussion), we also conducted functional

connectivity analyses of regions identified as responsive to the valence of faces and/or sentences.

## RESULTS

All subjects rated intended negative sentences negatively [mean =  $-2.875 \pm 0.55$ ;  $t(15) = 20.8$ ,  $p < .01$ ; one-sample  $t$  test tested vs. rating of “0”] and intended positive sentences positively [mean =  $3.06 \pm 0.63$ ;  $t(15) = 19.47$ ,  $p < .01$ ]. Valence ratings between these two sentence types were significantly different [ $t(15) = 24.35$ ,  $p < .01$ ]. There was no difference between negatively and positively cued faces in terms of valence ratings when presented alone postscan, without these preceding context sentences [ $t(15) = .3$ ,  $p = .7$ ].

### Negatively Versus Positively Cued Surprised Faces

Direct comparison of negatively versus positively cued faces revealed significantly greater activation within the left ventral amygdala (Figure 1A and Table 1;  $x = -15$ ,

$y = -7$ ,  $z = -15$ ;  $p = .000478$ , all reported  $p$ s are uncorrected). Figure 1B shows the magnitude of this effect across all presentations while also showing no differential responsivity to the sentence stimuli. This effect was reliably lateralized to the left [i.e., Hemisphere  $\times$  Valence interaction:  $F(1,15) = 8.01$ ,  $p = .013$ ]. Given previous reports of changes in amygdala responsivity with repeated presentations (Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Phelps et al., 2001; Phillips, Medford, et al., 2001; Whalen, Shin, et al., 2001; Wright et al., 2001; Whalen, Rauch, et al., 1998; Breiter et al., 1996), and because the present event-related design lends itself to the assessment of changes over time, Figure 1C parses this main effect over the three repeated presentations of each stimulus within scan. Note that all responses at this locus within the left ventral amygdala habituated over time. Indeed, responses here discriminated between negatively versus positively cued surprised faces at their second presentation, due to a more rapid habituation rate for positively cued faces.

No regions of the amygdala were more responsive to positively versus negatively cued surprised faces (all

**Table 1.** Other Areas of Activation for the Main Contrasts

Brain Regions	Talairach Coordinates			<i>p</i> values (uncorrected)
	<i>x</i>	<i>y</i>	<i>z</i>	
<i>Negatively-cued–Positively-cued faces</i>				
Amygdala (L)	-15	-7	-15	.000478
Fusiform gyrus (L: BA 20)	-28	-32	-13	.000027
Inferior frontal cortex (R: BA 44)	59	8	18	.00008
Medial orbital gyrus (L)	-15	8	-15	.00017
Parahippocampal gyrus (L: BA 36)	-35	-8	-22	.00000021
Piriform cortex (R: BA 34)	24	4	-20	.000085
Precentral gyrus (L: BA 4)	-46	-12	42	.00001
Superior temporal cortex (R: BA 22)	41	6	-14	.000015
<i>Negative–Positive sentences</i>				
Inferior frontal cortex (R: BA 45)	47	32	4	.00000065
Inferior temporal gyrus (L: BA 20)	-46	-18	20	.000013
Ventrolateral prefrontal cortex (R: BA 47)	34	32	-8	.000049
<i>Positive–Negative sentences</i>				
Superior temporal cortex (L: BA 22)	-44	7	-22	.000029
Thalamus (R)	12	-25	11	.000018
Ventromedial prefrontal cortex (R: BA 24)	5	19	-6	.00077
Ventromedial prefrontal cortex (R: BA 24)	4	29	-11	.00039

$ps > .3$ ). We did observe greater responsivity of the right vmPFC to positive versus negative faces (Brodmann's area [BA] 32;  $x = 6, y = 32, z = -5, p = .0092$ ) in a locus similar to Kim et al. (2003), but this activation did not survive statistical thresholding.

### Negative Versus Positive Sentences

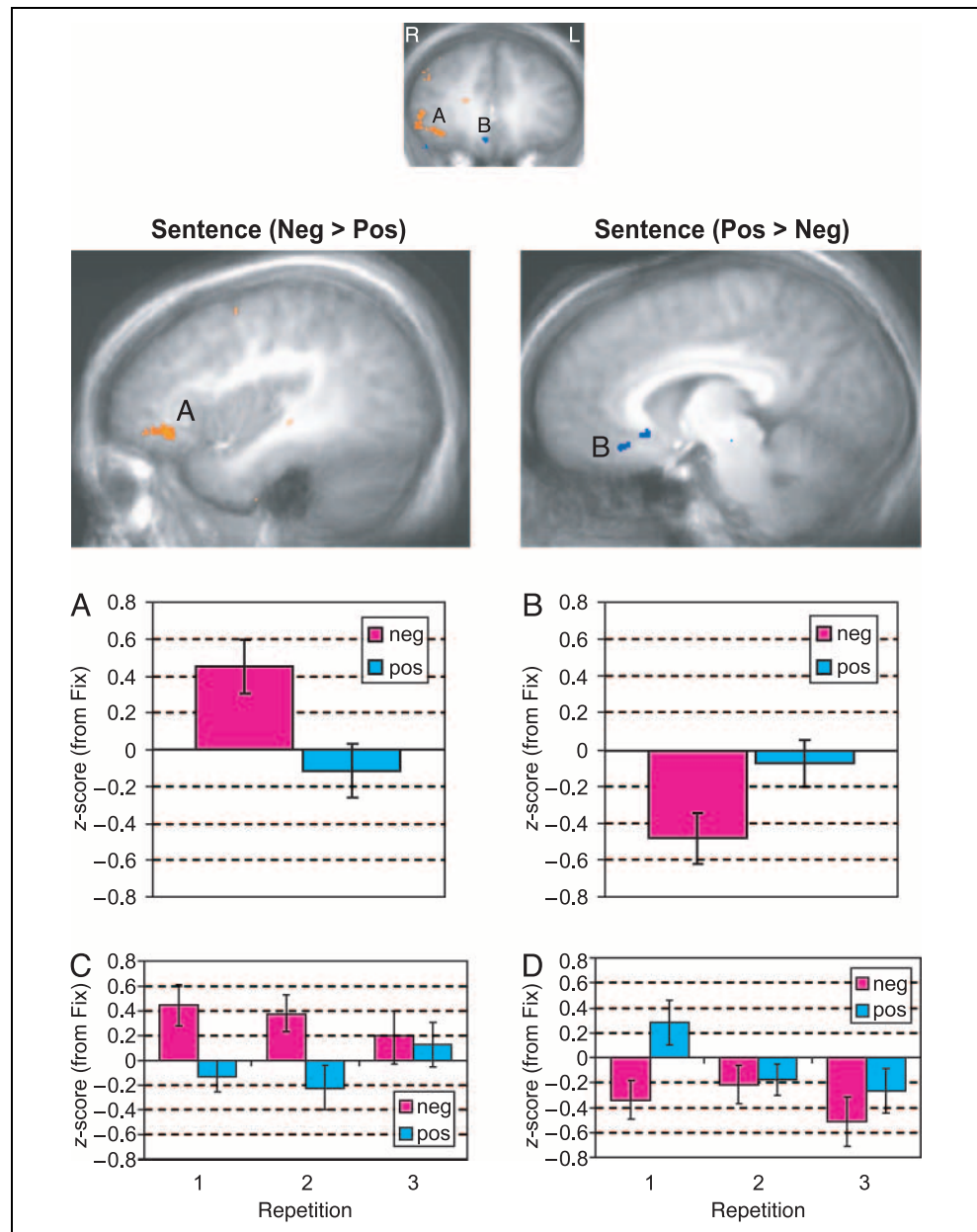
Greater response to negative versus positive sentences was observed in the right ventrolateral prefrontal cortex [vlPFC, BA 47; Figure 2A and Table 1;  $x = 34, y = 32, z = -8; p = .00049$ ]. This effect was reliably lateralized to the right [i.e., Hemisphere  $\times$  Valence interaction:  $F(1,15) = 9.14, p = .0086$ ]. Greater response to positive versus negative sentences was observed within the right vmPFC (BA 32; Figure 2B and Table 1;  $x = 4, y = 29,$

$z = -11; p = .00039$ ) and showed a trend toward lateralization to the right [i.e., Hemisphere  $\times$  Valence interaction:  $F(1,15) = 3.68, p = .074$ ]. For comparison with amygdala responsivity, Figure 2C–D parses these main effects over the three repeated presentations within scan.

### Functional Connectivity Analyses

Three primary regions of interest (ROIs) were chosen for functional connectivity analyses: the ventral amygdala (Figure 1A; from the contrast of negatively vs. positively cued surprised faces), the vmPFC (Figure 2A; from the contrast of positive vs. negative sentences), and the right vlPFC (Figure 2B; from the contrast of negative vs. positive sentences). These connectivity pattern maps

**Figure 2.** Statistical maps presented in sagittal and coronal planes showing significant signal changes within the ventrolateral prefrontal cortex (vlPFC) to negative versus positive sentences and within the ventromedial prefrontal cortex (vmPFC) to positive versus negative sentences. (A and B) Bar graphs depicting the nature of these signal changes within the vlPFC and vmPFC, respectively, from null fixation trials. (C and D) Bar graphs parsing these main effects by the three repeated presentations of each stimulus (average) within scan for vlPFC and vmPFC, respectively. Image parameters as in Figure 1.



are presented in Figure 3A–C. Figure 3A reveals that activity within the ventral amygdala locus responsive to negatively cued faces was positively correlated with responses within the dmPFC (BA 32/24 within the rostral/dorsal anterior cingulate) and the dorsal striatum (i.e., caudate). Figure 3B shows that activity within the vmPFC locus responsive to positive sentences was positively correlated with responses within the dmPFC (BA 32) and the ventral striatum (i.e., nucleus accumbens). Figure 3C shows that activity within the vlPFC locus responsive to negative sentences was positively correlated with responses within the dmPFC (BA 32) and the ventral amygdala, and negatively correlated with the vmPFC (BA 32/25). The diagram presented in Figure 3D summarizes the results of these three connectivity analyses emphasizing the observed correlations between the amygdala and the PFC.

Presented in the tables are the coordinates of loci for all reported contrasts (Table 1) and temporal correlations (Table 2).

## DISCUSSION

Here we demonstrated that negative versus positive verbal contextual information can modulate human amygdala responses to surprised facial expressions on a within-subject basis. Although negative and positive sentences were carefully matched for arousal value, situation, and length, greater amygdala responsivity was observed to negatively versus positively cued surprised faces. The fact that the amygdala was not responsive to the valenced sentences themselves emphasizes the modulatory nature of this effect. Connectivity analyses identified candidate cortical–subcortical systems involved, specifically implicating a region of the dmPFC (i.e., rostral/dorsal anterior cingulate) as a convergence and/or effector site mediating this effect.

### Human Amygdala Responses to Negatively Versus Positively Valenced Faces

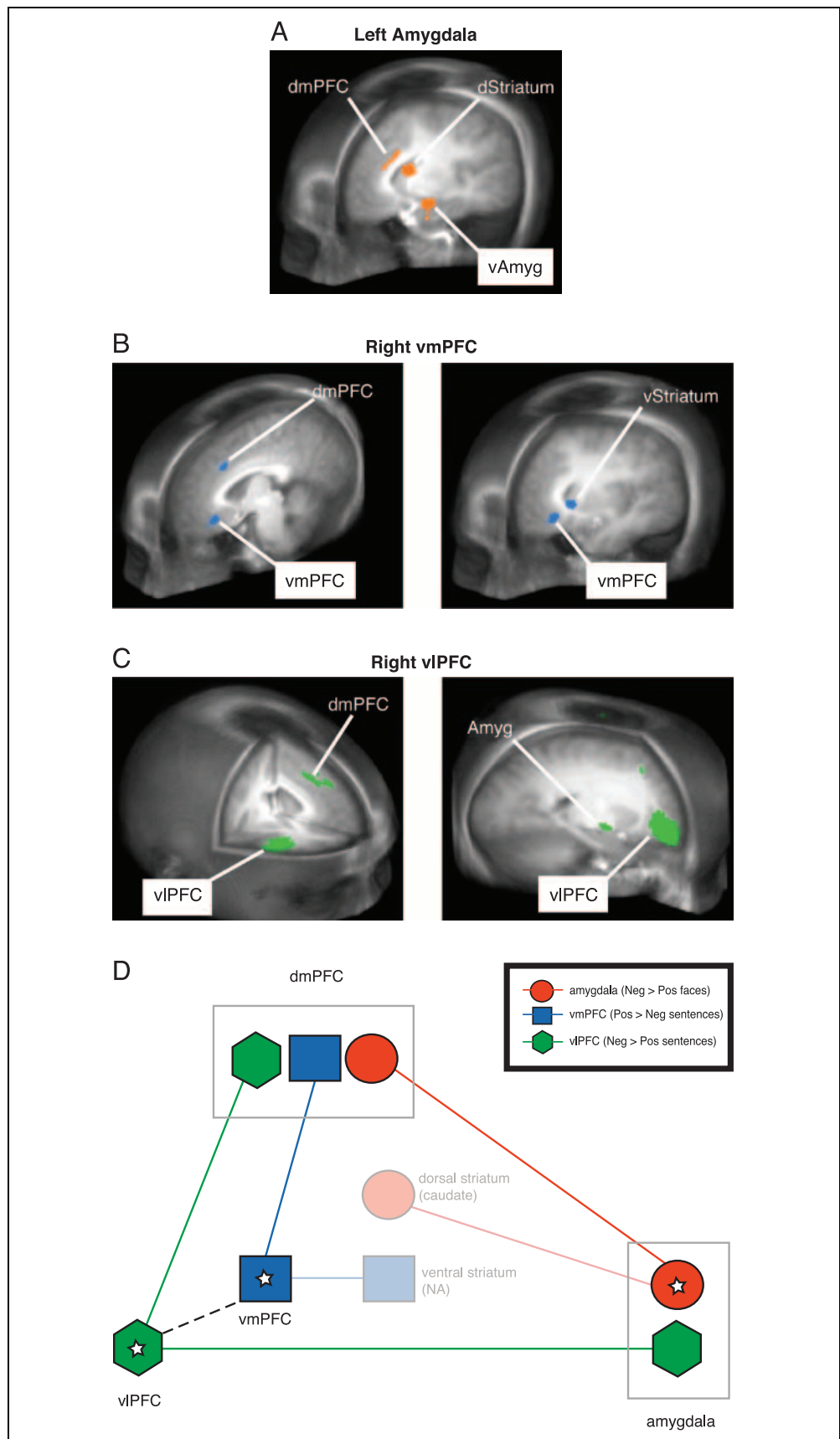
Negatively versus positively valenced sentences modulated amygdala responsivity to surprised facial expressions within the ventral amygdala. This finding is consistent with previous studies demonstrating ventral amygdala activation to negative facial expressions when directly contrasted with positive facial expressions (Whalen, Rauch, et al., 1998; Morris, Frith, et al., 1996). The present design extends these findings by using contextual information to produce a similar valence-based phenomenon, while holding the facial expression constant, thereby avoiding the possibility that ventral amygdala response differences were related to other potentially confounding differences between expression types (e.g., intensity, arousal, prior experience, facial features, contrast, luminance, etc.).

In a broader sense, these results converge with a psychological literature demonstrating that contextual information is a strong determinant of reactivity to specific predictive cues (e.g., Blanchard & Blanchard, 1969), particularly when those cues are ambiguous with respect to the valence of the outcome that they predict (Bouton, 1994). To elaborate, Bouton (1994) has argued that extinguished conditioned stimuli (CSs), are particularly sensitive to context manipulations due to their inconsistent reinforcement history with respect to predicted valence (e.g., tone predicted shock, now tone does not predict shock). The present demonstration of sensitivity to context lends credibility to our previous assertion that surprised faces are usefully compared to extinguished CSs; they evoke activity through an extinction-like PFC–amygdala circuitry (Kim et al., 2003) because they too are CSs that have ambiguous predictive information value with respect to valence (i.e., this expression has predicted both positive and negative outcomes in the past) and, therefore, evoke regulatory input from the PFC to the amygdala.

In the human, the ventral portion of the amygdala comprises the basolateral complex (BLC; Mai, Assheuer, & Paxinos 1997; also see Gloor, 1997). Animal studies demonstrate that the BLC discriminates between presented stimuli based upon their previously learned predictive value (LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; see Davis & Whalen, 2001) and engages in reciprocal communication with multiple cortical and subcortical systems concerning any changing predictive value, contextual underpinnings, and/or predicted outcomes (Milad & Quirk, 2002; Stefanacci & Amaral, 2002; Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Quirk et al., 2000; Schoenbaum, Chiba, et al., 1999; LeDoux, 1996; McDonald, Mascagni, & Guo, 1996; McDonald, 1991). Thus, the demonstration of ventral amygdala response to surprised faces based upon the valence of their associated contextual information is consistent with this role for the BLC.

The amygdala plays a role in many forms of biologically relevant learning, even learning about appetitive contingencies (Baxter & Murray, 2002; Gallagher & Holland, 1994). Indeed, responses to positively valenced facial expressions can be observed within the amygdaloid complex (Somerville et al., 2004; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Yang et al., 2002; Breiter et al., 1996). However, the spatial location of these activations within the amygdaloid complex, as well as the temporal profile of these responses, can differ from those observed to negative expressions (see Somerville et al., 2004). The present results demonstrate that at least a portion of the ventral amygdala shows preferential response to negatively versus positively valenced expressions when they are present in the same experimental paradigm and directly contrasted. In a general sense, these data support the notion that responsivity across the amygdaloid complex to a particular facial expression need not be absolute, but can depend on

**Figure 3.** Presentation of highlighted regions identified by functional connectivity analyses (see Methods for details) using the three primary main effect sites depicted in Figure 1 and Figure 2 (see Table 2 for a full list of identified sites). The label of the site that each analysis is based upon (“seed”) is highlighted with a white box. (A) Regions that were temporally correlated with the left ventral amygdala. (B) Temporal correlations with right vmPFC. (C) Temporal correlations with the right vIPFC. (D) A summary of the prefrontal–amygdala sites of interest identified by the temporal correlation analyses presented in Figure 1. Areas correlating with amygdala are presented in red, with the vIPFC in green, and with the vmPFC in blue. The fact these regions represent the basis of each of these connectivity patterns (“seed”) is signified by a star. Here we highlight in color prefrontal and amygdala regions that were the focus of our investigation. Solid lines = positive temporal correlations; Dashed lines = negative temporal correlations. Additionally identified striatal ROIs that were not predicted are presented as transparencies. This figure emphasizes that activity within the dmPFC was temporally correlated with all three main effect ROIs, potentially representing an effector or convergence site for sentence and face information.



**Table 2.** Other Areas Temporally Correlated with Three ROIs

<i>Brain Regions</i>	<i>Talairach Coordinates</i>			<i>p</i> values (uncorrected)
	<i>x</i>	<i>y</i>	<i>z</i>	
<i>Brain regions temporally correlated with the left amygdala</i>				
Amygdala (R)	13	-7	-15	.00000019
Anterior cingulate cortex (RL: BA 24/32)	7	9	34	.00000018
	-7	13	27	.000000016
Dorsal caudate nucleus (RL)	14	13	15	.000000007
	-16	8	16	.000000008
Putamen (RL)	26	4	0	.000000018
	-20	8	10	.000000008
Substantia nigra (RL)	5	-18	-14	.000000003
	-8	-16	-15	.000000003
Thalamus (RL)	4	-5	4	< .000000001
	-2	-7	2	.000000016
Ventrolateral prefrontal cortex (RL: BA 47)	31	29	-11	.00014
	-33	26	-13	.0000012
<i>Brain regions temporally correlated with the right ventromedial prefrontal cortex</i>				
Anterior cingulate cortex (L: BA 32)	-3	18	33	.0000038
Postcentral gyrus (L: BA 1)	-61	-20	37	.00018
Superior temporal cortex (R: BA 22)	41	2	-15	.00006
Ventral striatum (R)	15	21	-1	.00013
	-17	20	0	.00025
Ventrolateral prefrontal cortex (RL: BA 47)	32	22	-17	.0000052
	-35	23	-16	.0000031
<i>Brain regions temporally correlated with the right ventrolateral prefrontal cortex</i>				
Amygdala (RL)	21	-5	-6	.0000017
	-23	-7	-7	.00000068
Anterior cingulate cortex (RL: BA 24)	8	14	28	.000000009
	-6	16	25	.00000003
Anterior cingulate cortex (L: BA 32)	-5	25	38	.00000003
Caudate nucleus (RL)	5	3	13	.00000096
	-10	-4	14	.000000014
Inferior frontal cortex (R: BA 9)	37	16	27	.000000007
Inferior frontal cortex (R: BA 45)	43	23	7	.000000006
Insular (R)	30	14	-7	< .000000001
	-32	15	-3	.000000031
Pulvinar (L)	-5	-25	3	< .000000001
Substantia innominata (R)	28	-5	-6	.00000011

**Table 2.** (continued)

Brain Regions	Talairach Coordinates			<i>p</i> values (uncorrected)
	<i>x</i>	<i>y</i>	<i>z</i>	
Superior frontal cortex (R: BA 8)	8	38	41	< .000000001
	-1	27	49	.00000001
Thalamus (RL)	2	-20	11	.000000004
	-8	-19	13	< .000000001
Ventrolateral prefrontal cortex (L: BA 47)	-52	29	-5	.000000011
<i>Brain regions showing negative temporal correlation with the right ventrolateral prefrontal cortex</i>				
Ventromedial prefrontal cortex (R: BA 32)	10	31	-12	.00069
Ventromedial prefrontal cortex (R: BA 11)	2	22	-21	.00012

the information value of an expression in a given situation or context.

### Temporal Characteristics of Amygdala Responses

Because numerous studies have documented habituation of amygdala response to repeated presentations of facial expressions (Somerville et al., 2004; Phelps et al., 2001; Phillips, Medford, et al., 2001; Whalen, Shin, et al., 2001; Wright et al., 2001; Whalen, Rauch, et al., 1998; Breiter et al., 1996), we exploited the current event-related design to assess how amygdala response at this main-effect locus changed over time (Figure 1C). Note that the left ventral amygdala did not discriminate between negatively and positively cued faces at their first presentation, but that this discrimination emerged at their second repetition. Contrast this with the fact that the identified mPFC sites discriminated between the negative and positive contextual sentences at their first presentation (see Figure 2C–D).

These data are consistent with the notion that these signals observed over time within the left ventral amygdala may represent a compromise between feature-based amygdala responses to surprised faces and regulatory prefrontal responses concerning the nature of the valence of the event eliciting these expressions. To elaborate, we hypothesize that at their first presentation, the amygdala responds to the “potential” negativity of surprised faces presented in both valence conditions, despite the competing contextual information related to positively cued surprised faces. By their second repetition, the amygdala heeds the messages from the PFC and conserves resources during presentation of positively cued faces. These differing response slopes appear to be superimposed on a habituating response profile that resulted in significantly decreased responsivity at the third repetition in both conditions. That is,

within the present experimental context, left ventral amygdala BOLD responses to negatively cued surprised faces habituated after 12 stimulus presentations (i.e., two presentations each of six identities) compared to positively cued surprised faces, which habituated after six stimulus presentations (i.e., one presentation of the six identities).

### Issues of Laterality

In terms of laterality, the present valence effect was observed within the left ventral amygdala. In our previous study (Kim et al., 2003), individual differences in valence judgments of surprised faces were related to right ventral amygdala signal intensities, with greater signal levels associated with more negative judgments of surprise. Differences in the experimental design of these two studies might offer clues to the nature of this laterality difference. First, in the previous study, subjects ascribed valence judgments to surprised faces, whereas in the present study, valence was determined by contextual stimuli. Perhaps these different sources of threat-related information between the two studies underlies this laterality difference: perceived facial features activated the right amygdala in our previous study (see Morris, Öhman, et al., 1998) whereas verbal context activated the left amygdala in the present study (see Phelps et al., 2001).

As a related but distinct alternative, we would suggest that the predictive clarity of presented stimuli may be a useful heuristic when considering laterality differences in amygdala response to biologically relevant stimuli. To elaborate, though we did not predict it initially, we continue to observe right lateralized activations to fMRI subtractions that emphasize the ambiguous predictive value of a given facial expression (Kim et al., 2003; Whalen, Shin, et al., 2001). For example, our recent study (Kim et al., 2003) reported that fearful faces



unanimously rated as negatively valenced by all subjects (unambiguous valence) activated the left amygdala, whereas surprised faces variably rated as positively or negatively valenced (ambiguous valence) activated the right amygdala. In the present study, left amygdala activity was observed when valence was clearly determined. These data converge with hemispheric laterality models derived from data using lexical ambiguity tasks where the right hemisphere functions to allow flexibility in the consideration of numerous possible meanings for a given ambiguous word (e.g., homograph), while the left hemisphere focuses resources upon the most probable meaning of a word (Coney & Evans, 2000; Faust & Chiarello, 1998; Zaidel, Zaidel, Oxbury, & Oxbury, 1995). This interpretation is consistent with a purported role for the right hemisphere in ambiguity resolution (Burgess & Simpson, 1988). Thus, surprised faces showed greater right amygdala involvement when presented without contextual information in our previous study because there were multiple options (in terms of valence) that had to be considered. Here we document greater left amygdala involvement when the negative valence of the presented surprised face was “clearly” defined (see Podell, Lovell, Zimmerman, & Goldberg, 1995). Of course, disentangling clarity of valence from the ability to use language to achieve such clarity will be a challenge.

### **PFC Responses to Valenced Sentences**

We found signal intensities were greater to positive versus negative sentences in the right vmPFC, and greater to negative versus positive sentences in the right vlPFC. Previous studies have demonstrated similar valence-based dissociations between these two regions (O’Doherty, Critchley, Deichmann, & Dolan, 2003; O’Doherty, Winston, et al., 2003; Gottfried, O’Doherty, & Dolan, 2002; O’Doherty, Kringelbach, Rolls, Harnak, & Andrews, 2001; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001). This dissociation should not be considered absolute as different experimental designs can yield opposite effects (e.g., see Northoff et al., 2000). Indeed, although valence can be an important determinant of ventral PFC response, (a) these regions are also revealed within nonvalence based subtractions (Elliott, Dolan, & Frith, 2000) and (b) valence often interacts with response demands (O’Doherty, Critchley, et al., 2003) and/or the certainty of outcomes (Elliott et al., 2000) in determining responsivity within these regions.

More broadly, the present results are consistent with previous studies independently showing vlPFC response to negatively valenced stimuli and/or the inducement of negative emotional states (Levesque et al., 2003; Markowitsch, Vanderkerckhovel, Lanfermann, & Russ, 2003; Damasio et al., 2000; Dougherty et al., 1999; Kimbrell et al., 1999; Beauregard, Leroux, et al., 1998; Fredrikson, Wik, Fischer, & Andersson, 1995; George, Ketter, et al.,

1995; Pardo, Pardo, & Raichle, 1993) or vmPFC activation to positively valenced stimuli and/or states (Kim et al., 2003; Milad & Quirk, 2002; Quirk et al., 2000; Teasdale et al., 1999; George, Ketter, Parekh, Herscovitch, & Post, 1996).

### **Connectivity Analyses**

Figure 3 summarizes brain regions demonstrating temporal correlations with the amygdala, vmPFC, and vlPFC loci identified here. Tracing studies support the existence of strong reciprocal anatomical connections between the amygdala and these dorsal and ventral mPFC (Stefanacci & Amaral, 2002; McDonald et al., 1996; Amaral, Price, Pitkamen, & Carmichael, 1992; McDonald, 1991) and vlPFC regions (Ghashghaei & Barbas, 2002; McDonald, 1998). Note that the activity of all three regions was correlated with activity within regions of the dmPFC, suggesting its potential role as an effector or convergence site for sentence and face information, within the present study design. Involvement of this dmPFC region, clearly including the rostral/dorsal anterior cingulate, may be consistent with previous reports showing that emotionally valenced stimulus presentations activate this general region (Bush, Whalen, et al., 1998; Whalen, Bush, et al., 1998), as well as more unified theories implicating this anterior cingulate region in the integration and regulatory control of biologically relevant information processing (Bishop, Duncan, Brett, & Lawrence, 2004; Yamasaki, LaBar, & McCarthy, 2002; Shin et al., 2001; Bush, Luu, & Posner, 2000; Mayberg, 1997).

An important consideration when viewing the diagram in Figure 3D is that evidence of positive temporal correlations does not necessitate that these are excitatory connections. Recent studies documenting a dissociation between neural spikes and local field potential (LFP) activity (Mathiesen, Caesar, & Lauritzen, 2000; Mathiesen, Caesar, Akgoren, & Lauritzen, 1998) suggest that BOLD signal is related more to LFPs than neural activity (Logothetis, 2003; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Thus, an excitatory or inhibitory input will be observed as a signal increase. This same logic has implications for interpreting negative temporal correlations between two brain regions. For example, we observed a negative relationship between responses to positive sentences in the vmPFC and response to negative sentences in the vlPFC. Although this could represent evidence of an inhibitory connection, this would not necessarily be the case if BOLD signal reflects LFPs. Instead, this scenario would call for consideration of a third structure (see Logothetis, 2003), wherein functional control over one area is withdrawn in response to incoming activation from the other. In such a scenario, the present data suggest that the dmPFC could be one such candidate structure. Activation of vlPFC to negative sentences could activate the dmPFC, which in turn withdraws an excitatory input to the vmPFC. This scenario is

consistent with the finding that although the vmPFC main effect for positive > negative sentences included signal increases to positive sentences at their first repetition (Figure 2B), this main effect also comprised signal decreases to negative sentences, consistent with the notion of a withdrawal of a tonic excitatory input.

Activity at the amygdala locus that was more responsive to negatively valenced surprised faces was temporally correlated with dmPFC activity, consistent with our previous report based upon final averaged outcomes in response to blocked surprised faces (Kim et al., 2003). Thus, across two studies/methodologies, negative interpretations of surprised faces (either undetermined [previous study] or determined [present study]) produced correlated signal increases in the ventral amygdala and the dmPFC (i.e., rostral/dorsal anterior cingulate).

We did not observe inverse temporal correlations between activity within the amygdala and the vmPFC to surprised faces, in contrast to our previous report based upon spontaneous assessments of surprised faces (Kim et al., 2003). The presence of the contextual sentences may underlie differences between these two studies. To elaborate, the previously observed relationship between the amygdala and the vmPFC may have been based upon the ambiguity of valence inherent to surprised faces presented alone, and the contextual sentences in the present study alleviated this ambiguity and, thus, the need for this connectivity. Alternatively, without benefit of the sentences, subjects would have to rely on their past experiences with surprise (i.e., memory) to a greater degree. Milad and Quirk (2002) and Quirk et al. (2000) have elegantly demonstrated that vmPFC activity is related to the “memory” of extinction, not the process per se. Finally, the sentences may have provided an external, third-person event locus (i.e., that happened to them), whereas surprised faces presented alone might more readily engage in a self-referential mode of processing (i.e., what might happen to me?). Numerous studies have demonstrated that the mPFC is engaged more readily when biologically relevant processing is self-referential (Fossati et al., 2003; Wicker, Ruby, Royet, & Fonlupt, 2003; Johnson et al., 2002; Kelley et al., 2002; Zysset, Huber, Ferstl, & von Cramon, 2002; Gusnard, Akbudak, Shulman, & Raichle, 2001). Thus, in summary, the finding of vmPFC activation in our previous, but not the present, study could be related to differences in ambiguity of valence, reliance on memory process, whether a stimulus was self-referential, and/or the nature of vmPFC–amygdala connectivity.

### Limitations

The present data were collected within the context of a passive viewing paradigm (Somerville et al., 2004; Kim et al., 2003; Whalen, Shin, et al., 2001; Whalen, Rauch, et al., 1998). Future studies could and should seek to introduce tasks to these paradigms to allow

for the interpretation of BOLD signal responses in terms of measured behavior. The caveat here is that by imposing a task, one may lose the ability to measure what subjects would have spontaneously done with the presented stimuli. For example, Kim et al. (2003) demonstrated that subjects showed variability in their spontaneous interpretations of surprised faces during passive viewing, and, together, postscan valence ratings and amygdala–mPFC responsivity explained a good deal of this variability.

In addition, the amygdala is known to be one of a select group of brain regions that are particularly sensitive to task-induced signal decreases (Hariri, Mattay, et al., 2003; Lange et al., 2003; Gusnard & Raichle, 2001; Simpson, Drevets, Snyder, Gusnard, & Raichle, 2001; Simpson, Snyder, Gusnard, & Raichle, 2001; Bush, Luu, et al., 2000; Hariri, Bookheimer, & Mazziotta, 2000; Bush, Whalen, et al., 1998; Whalen, Bush, et al., 1998), a methodological point that complicates interpretation of signal changes in this region when a task is introduced. Given the infancy of fMRI and the relative paucity of data available concerning amygdala responsivity to facial expressions of emotion, we welcome both types of data (i.e., 1: passive viewing where one can study subject’s spontaneous strategies with proper debriefing and 2: instructed tasks where between-subject variability can be potentially minimized and signal changes can be correlated with behavior) to more fully inform the complex interactions that undoubtedly exist between measured signal changes in the brain, the task at hand (or lack thereof) and the constitution of the subject of study.

### Conclusions

The present study has demonstrated that left ventral amygdala response to surprised facial expressions can be modulated by contextual sentences, with greater responses observed to negatively versus positively cued surprised faces. Because surprised faces were common to both valence conditions, the present valence effect avoids confounds inherent to comparing different facial expressions. We also found that the vmPFC and the vlPFC were differentially responsive to positive and negative sentences, respectively. Functional connectivity analyses provided evidence that a region of the dmPFC (rostral/dorsal anterior cingulate) was temporally correlated with regions responsive to both faces and sentences, suggesting a convergence or effector function for this region.

These findings join a diverse list of experimental manipulations in animal and human subjects implicating the PFC in regulatory control over the amygdala, including studies assessing extinction processes (Barrett, Shumake, Jones, & Gonzalez-Lima, 2003; Milad & Quirk, 2002; Quirk et al., 2000; Garcia, Vouimba, Baudry, & Thompson, 1999; Morgan & LeDoux, 1995; Morgan, Romanski, et al., 1993), stimulus value changes (Schoenbaum,

Setlow, Sadoris, & Gallagher, 2003; Baxter & Murray, 2002; Rolls, 1999; Schoenbaum, Chiba, et al., 1999), decision-making (Bechara, Damasio, Damasio, & Lee, 1999), labeling of affective stimuli (Hariri, Mattay, et al., 2003; Hariri, Bookheimer, et al., 2000), directed emotion regulation (Schaefer et al., 2003; Ochsner, Bunge, Gross, & Gabrieli, 2002; Beauregard, Levesque, & Bourgouin, 2001), regulation of anxiety-related behavior (Heidbreder, Thompson, & Shippenberg, 1996), passive avoidance learning (Jinks & McGregor, 1997), perseverative responding (Passetti, Levita, & Robbins, 2003; Dias & Aggleton, 2000), and reversal learning (Li & Shao, 1998). Taken together, these studies support the more generalized involvement of PFC–temporal lobe interactions in behavioral flexibility (Fellows & Farah, 2003; Killcross & Coutureau, 2003; Dias & Aggleton, 2000; Bechara et al., 1999; Rolls, 1999; Morgan & LeDoux, 1995; deBruin, Sanchez-Santed, Heinsbroek, Donker, & Postmes, 1994).

## METHODS

### Subjects

Sixteen right-handed (Oldfield, 1971) adults (8 women, mean age:  $22.94 \pm 3.66$ ) were recruited for this experiment. All subjects underwent a brief clinical interview to ensure that they were without significant psychiatric, neurological, or medical illness. This investigation was conducted in accordance with the guidelines of the Human Subjects Committee of the University of Wisconsin—Madison.

### Stimuli

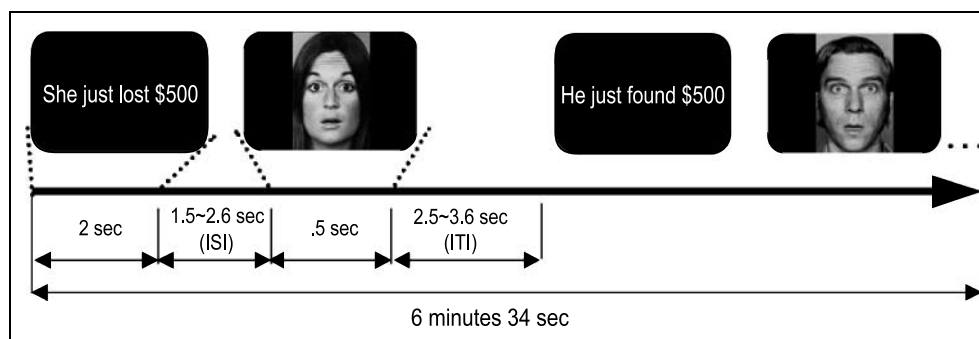
All visual stimuli were presented through specialized fiber-optic goggles (AVOTEC, Stuart, FL). Face stimuli (Ekman & Friesen, 1976) consisted of surprised facial expressions of 12 individuals, six women (stimuli used were C, JM, MF, MO, SW, PF, EM, GS, JB, JJ, PE, WF). Sentence stimuli were derived from pilot data obtained from 12 subjects (6 women) from the same university subject pool. These subjects provided subjective valence and arousal ratings of 24 candidate sentences. The va-

lence scale used ranged from  $-4$  (very negative) to  $0$  (neither negative nor positive) to  $+4$  (very positive); the arousal scale ranged from  $1$  (the least amount of emotional arousal I have ever felt) to  $5$  (medium emotional arousal) to  $9$  (the greatest amount of emotional arousal I have ever felt). Based on these ratings, we selected 12 sentences (6 positive and 6 negative) that were disparate for valence ratings but matched for arousal ratings (see Appendix). These sentences were then administered to an additional 12 subjects (6 women). Mean ratings were as follows: Valence: positive sentences =  $2.57 \pm 0.60$ , negative sentences =  $-2.50 \pm 0.41$ ; Arousal: positive sentences =  $5.19 \pm 1.36$ , negative sentences =  $5.0 \pm 1.17$ . Valence ratings were significantly different between intended positive and negative sentences [ $t(11) = 18.71$ ,  $p = .000000001$ ], whereas arousal ratings did not differ [ $t(11) = 0.45$ ,  $p = .66$ ]. These data were highly consistent with ratings of these 12 items from the first group of 12 subjects [Valence:  $t(11) = 14.2$ ,  $p = .00003$ ; Arousal:  $t(11) = .185$ ,  $p = .86$ ]. Thus, negative and positive sentences that were comparable in length and situations being described were shown to be comparable in terms of arousal level across two samples. Sentences are presented in the Appendix.

### Paradigm

During two scans, each of which lasted 6 min and 34 sec, subjects passively viewed individual presentations of sentences and faces, or a fixation point on an otherwise blank screen. In a single trial, each sentence, which described either a positive or negative context, was presented for 2 sec, and preceded a surprised face presented for 0.5 sec. The interval between the offset of a sentence and the onset of a face (i.e., interstimulus interval [ISI]), was pseudorandomly varied between 1.5 and 2.6 sec, and the interval between the offset of a face and the onset of a sentence from the next trial (i.e., intertrial interval [ITI]) was pseudorandomly varied between 2.5 and 3.6 sec (see Figure 4). This “jittered” timing scheme allowed us to separately model overlapping hemodynamic responses to face and sentence stimuli (see Buckner et al., 1996). Each face and sentence was repeated three times within a single scan.

**Figure 4.** Schematic timeline for each of two trial types (negative and positive).



Therefore, each scan consisted of 18 negative and 18 positive condition trials, as well as 12 null trials (i.e., fixation presentation, see Buckner et al., 1996 for details). Trials were presented in a pseudorandom order.

The identities of six of the surprised faces were always paired with negative contextual sentences, while the other six faces were always paired with positive sentences, and these sentence–identity pairs were preserved throughout all trials. The identities within each valence condition were switched for the other half of the subjects, to ensure that the contrast in fMRI signals between negatively and positively cued surprised face trials was not due to the intrinsic features of certain faces. Note that we deliberately did not include a neutral sentence/neutral face condition. This would be a very interesting study in its own right, but does not meet the criteria we set for the present study of preserving the same expression category within each valence condition.

Upon exiting the scanner, subjects were again presented with the same face and sentence stimuli separately, and asked to provide a valence rating based on a scale ranging from  $-4$  (very negative) to  $0$  (neither negative nor positive) to  $+4$  (very positive).

### fMRI Image Acquisition

Subjects were scanned with a 3.0 Tesla MRI scanner (General Electric SIGNA; Waukesha, WI) with high-speed imaging gradients and a quadrature head coil. A whole-brain high-resolution T1-weighted anatomical scan (3-D IR-prepped fast gradient echo;  $256 \times 256$  in-plane resolution, 240 mm FOV;  $124 \times 1.1$  mm axial slices) was acquired for transformation and localization of functional data to Talairach space (Talairach & Tournoux, 1988). An EPI sequence (TR/TE/Flip = 2000 msec/30 msec/ $60^\circ$ ) was used to collect functional data, with 26 contiguous 3-mm-thick coronal oblique slices (0.5 mm interslice gap;  $64 \times 64$  in-plane resolution, 180 mm FOV). As our emphasis was on studying the amygdala and the mPFC, slices were centered over the amygdala and tilted  $\sim 30^\circ$  in an anterior direction. Thus, slices covered most of the frontal cortex (missing only the most anterior frontal pole) and the temporal cortex (including the amygdala and hippocampus), but not the parietal or occipital cortex.

### fMRI Data Analysis

AFNI software (Cox, 1996) was used for data analysis. Raw functional BOLD images were motion-corrected and smoothed using a gaussian kernel with 6 mm FWHM. BOLD responses to six stimuli [Condition (negative, positive, null)  $\times$  Stimulus type (sentence and face)] were modeled using a train of delta functions marking variable stimulus onsets convolved with an ideal hemodynamic response function. Using a general linear model (GLM) with these six regressors, we then

generated linear contrast maps (i.e., negative–positive, negative–null, and positive–null for both faces and sentences). The linear contrast maps were transformed into  $z$ -score maps, and averaged across scans. The averaged  $z$ -score maps were spatially normalized into Talairach space for group analysis using one-sample  $t$  tests. Laterality effects were tested by comparing peak response for main effects to the mirror locus in the opposite hemisphere.

For functional connectivity analyses, we tested loci from the three main findings: the amygdala (Figure 1A), the vlPFC (Figure 2A), and the vmPFC (Figure 3B). We extracted a time series from each individual's smoothed data corresponding to the position of the maximum group effect. The extracted time series was used as a reference time series to perform cross correlation analysis on each individual's scan. Each resulting functional image obtained from cross correlation analysis was averaged across scans and analyzed for the group using a one-sample  $t$  test.

Given our focus on responses within the amygdala and the mPFC, we first defined the anatomical boundaries of these two search volumes separately, consistent with previous correlational studies focusing on these regions (Anderson et al., 2003; Kim et al., 2003; Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002; Patterson, Ungerleider, & Bandettini, 2002). The boundaries of the amygdala are clearly defined in the Mai et al. (1997) human medial temporal lobe atlas presented in Talairach space. Based on this atlas, the amygdala/substantia innominata (SI) region constituted a search volume of  $\sim 3500$  mm<sup>3</sup> bilaterally. Because we discuss response differences based upon our a priori designation of ventral amygdala versus more dorsal amygdala/SI (see Somerville et al., 2004; Kim et al., 2003; Whalen, Shin, et al., 2001; Whalen, 1998; Whalen, Rauch, et al., 1998), we note that we use a dividing line of  $z = -10$  in Talairach space to define this distinction. Based upon our previous finding assessing mPFC interactions with the amygdala (Kim et al., 2003), we restricted our mPFC search volume to  $\sim 16,000$  mm<sup>3</sup>. For all other activations in the present study, we used the whole acquired brain volume as a search area, which constituted  $\sim 925,780$  mm<sup>3</sup>. The maximally activated voxels of all reported results survived statistical thresholding at  $p < .05$ , corrected for multiple comparisons as stipulated by Monte Carlo simulations based on the search areas specified above.

### Signal Quality

Susceptibility-related signal dropout attributable to B0 inhomogeneity is of particular concern within the ventral PFC and the amygdala (Ojemann et al., 1997). We addressed this issue as follows. First, our acquisition parameters were selected to minimize susceptibility artifact in that (1) use of relatively small and roughly isotropic

voxels reduces intravoxel signal dephasing; (2) data acquired in coronal slices minimize throughplane signal dephasing; and (3) use of a relatively short echo time (TE) minimizes phase dispersion at the time of echo.

In addition, use of random effects analyses protected these reported results from the influence of transient values across subjects. That said, we note that there were no outliers (i.e.,  $\pm 2 SD$  from group mean) at the amygdala or vPFC locus and only one outlier at the vmPFC locus. Results were identical when this outlier was excluded. In addition, our search locations within the amygdala and the PFC were constrained by known anatomical connections between the two (see Discussion) and our previous results (Kim et al., 2003; e.g., the observed vmPFC locus showing greater responsivity to positive sentences is an almost identical location to our previous finding showing greater responsivity to surprised faces interpreted as positive in valence).

A separate issue related to susceptibility artifact is the artificial “edge” that is created. Movement on the part of subjects that exceeds the area of one voxel can create an artifactual “response” at such an edge. All subjects’ head movement was constrained through the use of tightly packed head pillows. Based upon the movement correction algorithms enacted through AFNI, we verified that all subjects moved less than 1.5 mm (i.e., half a voxel) in all directions (A–P, R–L, and I–S). In addition, it should be noted that the effects reported here were not located at the edge of signal dropout, that is, there was no significant difference in baseline signal intensity between reported voxels and immediately subadjacent voxels. Thus, it is not likely that the movement could have artificially created the observed signal changes. These precautions suggest that statistically significant differences in activity between positive and negative conditions could be detected despite the suboptimal signal quality associated with these medial temporal and ventral frontal regions.

## APPENDIX

<i>Positive Sentences</i>	<i>Negative Sentences</i>
She just found \$500	She just lost \$500
He just saw his son being born	He just saw his son being killed
She just found her wedding ring	She just lost her wedding ring
His baby just said her first word	His baby just fell off her chair
She just received an A on her paper	She just received an F on her paper
He just got promoted at his job	He just got fired from his job

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The data reported in this experiment have been deposited in the fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2004-1173R.

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