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Functional neuroanatomy of aversion and its anticipation

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The capacity to anticipate aversive circumstances is central not only to successful adaptation but also to understanding the abnormalities that contribute to excessive worry and anxiety disorders. Forecasting and reacting to aversive events mobilize a host of affective and cognitive capacities and corresponding brain processes. Rapid event-related functional magnetic resonance imaging (fMRI) in 21 healthy volunteers assessed the overlap and divergence in the neural instantiation of anticipating and being exposed to aversive pictures. Brain areas jointly activated by the anticipation of and exposure to aversive pictures included the dorsal amygdala, anterior insula, dorsal anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex (DLPFC), and right posterior orbitofrontal cortex (OFC). Anticipatory processes were uniquely associated with activations in rostral ACC, a more superior sector of the right DLPFC, and more medial sectors of the bilateral OFC. Activation of the right DLPFC in anticipation of aversion was associated with self-reports of increased negative affect, whereas OFC activation was associated with increases in both positive and negative affect. These results show that anticipation of aversion recruits key brain regions that respond to aversion, thereby potentially enhancing adaptive responses to aversive events.

Introduction

Signals preceding aversive events often serve to forecast impending danger, doom, or otherwise undesired outcomes. Anticipating negative events is a key component of worry and can be adaptive, leading to behavioral, emotional, and physiological adjustments in preparation for or prevention of aversive outcomes. The anticipation of aversion entails multiple affective and cognitive constituents, including threat detection, elicitation of unpleasant affect and anxiety, regulation of unpleasant emotions, attention to the expected source of the aversion, memory of relevant prior aversive events, and autonomic activity and initiation of motor programs to prime the organism for action and behavioral withdrawal. Unfortunately, anticipation and worry can become excessive and dysfunctional, a feature of various forms of psychopathology (e.g., panic disorder, generalized anxiety disorder, social anxiety disorder), and may evoke these anticipatory and response mechanisms unnecessarily.

Building on knowledge accrued from prior research identifying the functional neuroanatomy of processing aversive stimuli (Penfield and Faulk, 1955; Tomarken et al., 1990; Wheeler et al., 1993; Phillips et al., 1997, 1998, 2003, 2004; Davidson and Irwin, 1999; Simpson et al., 2000; Calder et al., 2001; Davis and Whalen, 2001; Ostrowsky et al., 2002; LeDoux, 2002; Bentley et al., 2003; Murphy et al., 2003; Wicker et al., 2003), research efforts can now turn to novel experimental designs that allow for the dissection of the various constituent components, such as anticipatory and reactivity processes (Chua et al., 1999; Ploghaus et al., 1999; Ueda et al., 2003; Wager et al., 2004). Research on anticipating pain, shock, and pharmacologically induced panic has implicated the insula and ACC (Chua et al., 1999; Javanmard et al., 1999; Ploghaus et al., 1999, 2003; Sawamoto et al., 2000; Craig, 2003; Wager et al., 2004; Lorenz et al., 2005). Also relevant is the extensive literature on fear conditioning (Davis, 1992; LeDoux, 2002), including neuroimaging studies that have reported amygdala activation to a paired conditioned stimulus (CS+) on trials when the unconditioned stimulus was not presented (Büchel et al., 1998; LaBar et al., 1998).

This rapid event-related fMRI study utilized warning cues that predicted aversive pictures to assess activation in five brain regions serving functions relevant to the anticipation of and exposure to aversion, including the amygdala in the detection of motivationally salient events (Davidson and Irwin, 1999; Davis and Whalen, 2001), insula and ACC in the integration of sensory, affective, cognitive, autonomic, and motor processes (Augustine, 1996; Price, 2000; Critchley et al., 2000, 2002b, 2004, 2005; Craig, 2002, 2003; Singer et al., 2004), right DLPFC in withdrawal-related unpleasant affect (Davidson and Irwin, 1999; Davidson, 2002; Nitschke and Heller, 2002), and OFC in decoding the affective value of a stimulus or event (Rolls, 1999, 2004; Nitschke et al., 2004). Accordingly, we predicted that these five hypothesized areas would activate both in anticipation of and response to

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the aversive pictures. In addition, we tested whether subregions of these areas would show preferential activation for anticipatory processing, as has been reported for the insula, ACC, DLPFC, and OFC (e.g., Murtha et al., 1996; Ploghaus et al., 1999, 2003; O'Doherty et al., 2002; Wager et al., 2004). Finally, we hypothesized that right DLFPC activation would be associated with a self-report measure of withdrawal-related unpleasant affect (Davidson, 2002; Nitschke and Heller, 2002) and that OFC activation would be associated with pleasant and unpleasant affect (Rolls, 1999; Nitschke et al., 2004).

Materials and methods

Subjects

Subjects were 21 right-handed undergraduate students (11 women and 10 men, mean age 19) who responded to flyers posted in the Department of Psychology at the University of Wisconsin-Madison. They were free of any medical or neurological problems, took no medications, and had no current psychiatric diagnoses as determined by the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1996). All subjects gave informed consent in accord with study approval by the Human Subjects Committee of the University of Wisconsin Medical School and were paid for their participation.

Experimental paradigm and stimuli

As shown in Fig. 1, each trial began with a 0.5-s warning cue (minus sign for aversive pictures, circle for neutral pictures) followed by a 2.5-s or 4.5-s black screen (pseudo-randomized within valence) and then two contiguous 0.5-s presentations of either aversive or neutral pictures. Another black screen for 16 or 18 s ended each 22-s trial. This trial structure was selected in an attempt to optimize methodological parameters for effectively distinguishing anticipation and picture reactivity periods while keeping subjects engaged (Ollinger et al., 2001). The epoch between the cue and picture was kept short in order to minimize any working-memory component that might interfere with the reaction to the cue. The use of either 2.5 or 4.5 s as the delay between the cue and picture allowed differentiation of hemodynamic response due to the cue from that due to the picture. The entire trial length was relatively long (22 seconds), so that the hemodynamic response to the picture could return to baseline before the onset of the subsequent cue. In addition, the use of an ITI not evenly divisible by the 3-s TR resulted in a temporal jitter, yielding an effective time resolution of 1 s.

Subjects were explicitly instructed about the cue–picture contingency at the start of the experiment. No response was required of subjects during this passive viewing task. There were 42 trials (21 aversive and 21 neutral presented in pseudo-random order) in each of the 3 functional scans of the fMRI experiment. Each functional scan began with a 30-s black screen resulting in a scan length of 16:09, with a total scanning time of 48:27.

During the fMRI experiment, subjects saw 252 pictures selected from the International Affective Picture Set (Lang et al., 1999), with no picture shown more than once. Based on published norms (Lang et al., 1999), pictures with the most unpleasant valence ratings and highest arousal ratings comprised the aversive set, which primarily included photographs of mutilated bodies and attack scenes. Neutral pictures selected (e.g., household items) had neutral valence ratings and low arousal ratings.

fMRI acquisition

Anatomical and functional images were acquired on a General Electric EchoSpeed 1.5 T scanner (Milwaukee, WI) with a standard quadrature birdcage headcoil. Whole-brain anatomical images were acquired using an axial T1-weighted 3D spoiled gradient-recalled echo scan [SPGR; TR/TE = 35/8 ms, flip angle (α) = 30°, number of excitations (NEX) = 1, field of view (FOV) = 24 × 24 cm, matrix = 256 × 192, slice thickness/gap = 1–1.2/0 mm, 124 slices]. Using a gradient-echo pulse sequence for detecting blood oxygen level-dependent (BOLD) contrast, coronal T2*-weighted echo-planar scans (EPI; TR/TE = 3000/50 ms, α = 90°, NEX = 1, FOV = 24 × 24 cm, matrix = 64 × 64, slice thickness/gap = 7/1 mm, in-plane resolution = 3.75 × 3.75 mm) provided whole-brain functional images via 23 interleaved slices. A Silent Vision system (Avotec, Inc., Jensen Beach, FL) displayed stimuli via a pair of

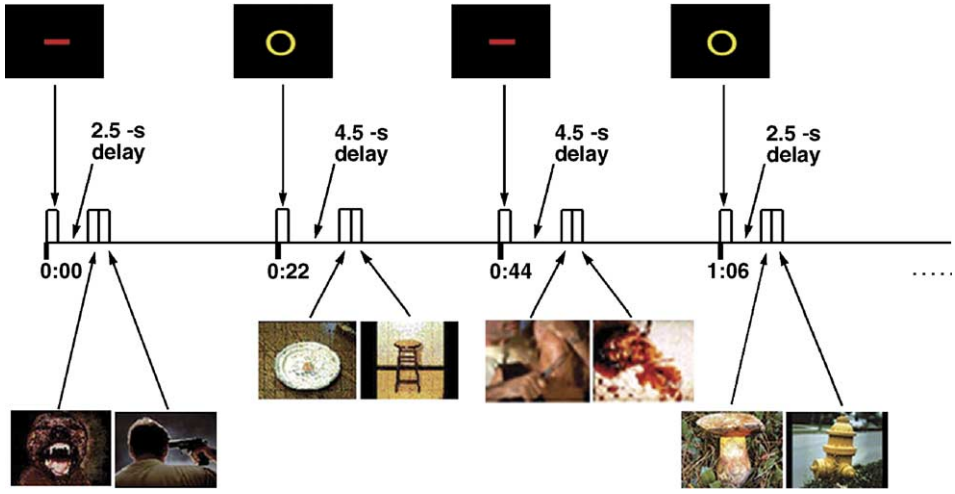
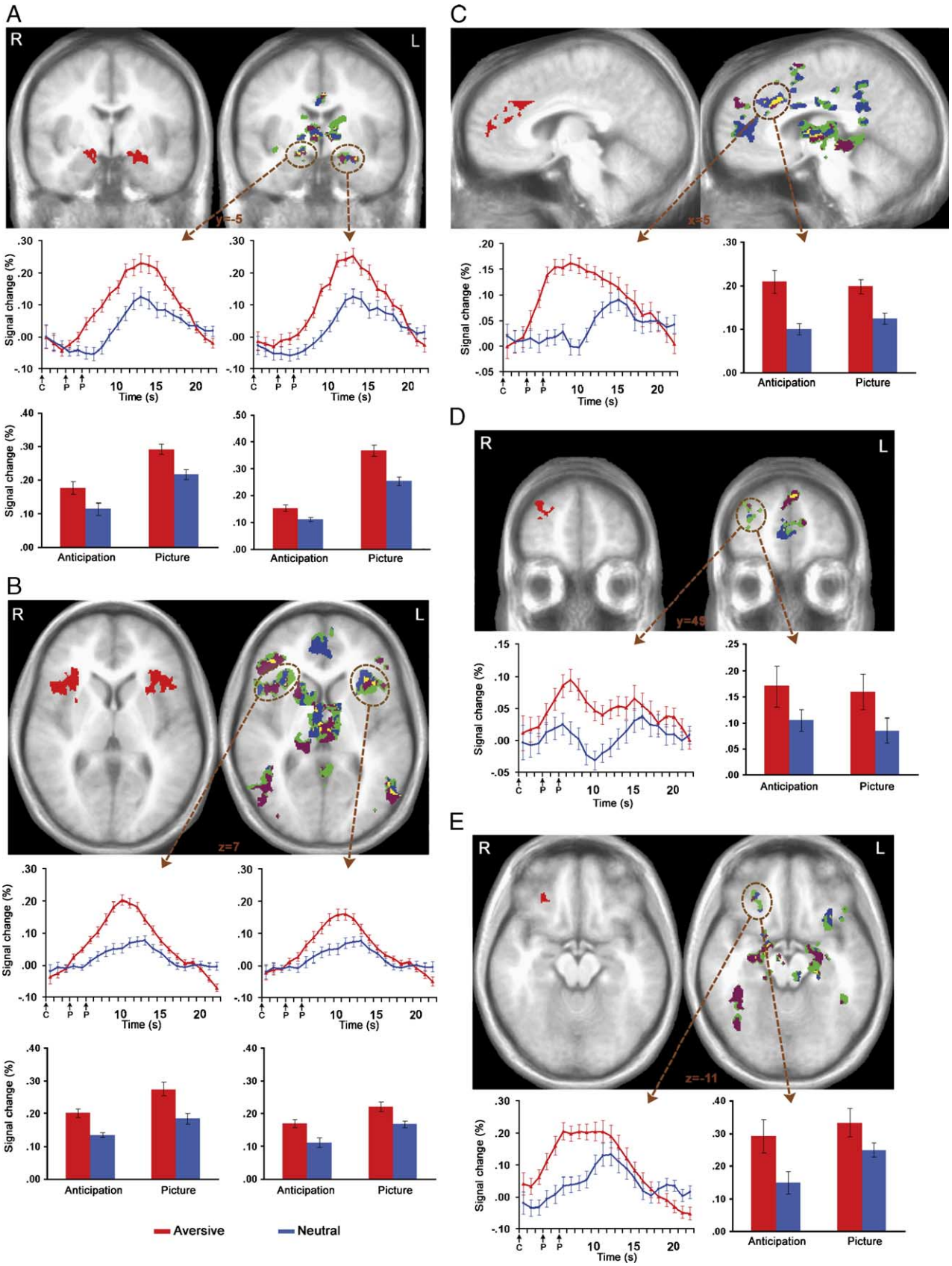


Fig. 1. Experimental design. Presentation of a 0.5-s visual warning cue at the beginning of a trial preceded the presentation of two contiguous 0.5-s pictures after an interval of 2.5 or 4.5 s. A minus sign invariably predicted aversive pictures, and a circle invariably predicted neutral pictures. The duration of each trial was 22 s, and there were 42 trials (21 aversive, 21 neutral) in each of three functional scans, with all pictures shown only once.


A
R
L
y=-5
Signal change (%)
Time (s)
C
P
P
Anticipation
Picture
B
z=7
C
x=-5
D
y=49
E
z=-11
Aversive
Neutral

stereoscopic goggles, and head movement was restricted using a customized bite bar, which consisted of dental impression compound affixed to an acrylic plate. Goggles and the bite bar were mounted directly to the headcoil. Approximately 1 week before the fMRI experimental session, all subjects were positioned in a mock MRI scanner including headcoil, goggles, bite bar, and digitized scanner sounds. They then viewed an abbreviated version of the experimental paradigm, with different pictures from those shown at the fMRI experimental session. This simulation session served to both acclimate subjects to the fMRI environment and to reinforce the cue–picture stimulus contingency.

fMRI analysis

Implemented via Analysis of Functional Neural Images version 2.31 software (AFNI; Cox, 1996), data processing steps included image reconstruction in conjunction with smoothing via a Fermi filter, 6-parameter rigid-body motion correction, removal of skull and ghost artifacts, and application of a high-pass temporal Fourier filter that removed frequencies slower than 0.014 Hz (i.e., slower than double the 22-s ITI). The time series was modeled with a least-squares general linear model (GLM) fit to an ideal hemodynamic response function, and the resultant beta-weights were converted to percentage signal change. During the GLM fit, the time-to-onset of response was allowed to vary independently for each voxel from 0 to 4 s, and the time lag selected was used for both the cue and picture stimuli. This variable onset allows for sensitivity to the varying blood perfusion rates across the brain, while fixing the time lag as the same for both cue and picture ensures that the two responses are properly separated and estimated. The percentage signal change maps from the GLM were Gaussian-blurred with full width at half maximum (FWHM) = 2 mm and transformed into the standardized Talairach space via identification of anatomical landmarks on the high-resolution SPGR (Talairach and Tournoux, 1988).

To test the main hypothesis that the amygdala, insula, ACC, right DLPFC, and OFC would activate to the aversive pictures and in anticipation of them, a conjunction analysis was performed. First, voxel-wise whole-brain Student's paired t tests compared aversive to neutral trials for the anticipation and picture periods separately. Monte Carlo simulations were then run to correct for multiple testing (Ward, 2000). Specifically, the spatial correlation of the input data and an uncorrected P value threshold of 0.005 resulted in a minimum cluster size of 362 mm^3 for the anticipation period t test and 399 mm^3 for the picture period t test to achieve a corrected map-wise $P < 0.05$. The conjunction map was constructed by taking the union of two statistical parametric maps (i.e., a voxel-level AND operation; Nichols et al., 2005) and applying the larger of the above cluster extent thresholds (Liu et al., 2003). The joint probability threshold was set at a P value of 0.005. This conjunction procedure yielded a mask containing only those voxels that were significantly activated above $t = 1.91$ ($P = 0.0707$) in each of the two contrasts, such that the probability of finding a voxel that is independently significant in each and both contrasts (i.e., the joint probability) can be estimated by multiplying the probabilities for each contrast: $0.0707 \times 0.0707 = P < 0.005$ (Allan et al., 2000; Cabeza et al., 2002; Liu et al., 2003; Dolcos et al., 2004). Overlapping thresholded regions that met the above criteria and fell within the anatomical boundaries of each of the five hypothesized regions (Talairach and Tournoux, 1988; Lancaster et al., 2000), as implemented in AFNI, were the focus of this conjunction analysis (Knutson et al., 2001; Ganis et al., 2004).

In addition, a whole-brain Period (Anticipation, Picture) × Valence (Aversive, Neutral) repeated-measures ANOVA was performed. To provide another test of the hypothesis that the five a priori brain regions would activate both in anticipation of and response to the aversive pictures, we constructed a statistical parametric map for the Valence main effect. To test whether any of the hypothesized five areas would activate primarily to the anticipation of aversive pictures rather than in response to them, we constructed a statistical parametric map for the Period × Valence interaction effect. Monte Carlo simulations were again run to correct for multiple testing. The spatial correlation of the input data and an uncorrected P value threshold of 0.005 resulted in a minimum cluster size of 381 mm^3 to achieve a corrected map-wise $P < 0.05$. For clusters meeting the corrected P value criterion, the average percentage signal change value was extracted for each condition and subject, and the values entered into post hoc analyses using t tests to determine the source of the significant effect. To test for sex differences, these average percentage signal change values were entered into a Sex × Period × Valence repeated-measures MANOVA (Keselman, 1998). The same statistical procedure was also applied to test for sex differences in the clusters identified by the conjunction analysis above.

To test the hypothesized lateralization of right DLFPC activation, significant right DLPFC clusters were dilated 250% and used to identify the homologous cluster in the left DLPFC.

Fig. 2. Activations during both the anticipation of and reactivity to aversion. The figure illustrates greater activation for aversive than neutral trials across anticipation and picture periods in (A) bilateral dorsal amygdala, (B) bilateral anterior insula, (C) anterior cingulate cortex, (D) right dorsolateral prefrontal cortex, and (E) right orbitofrontal cortex. The first brain image in each panel displays the results of the conjunction analysis, which identifies areas that activate more for aversive than neutral trials during both the anticipation period and the picture period when analyzed separately. Illustrated are activations within the anatomical boundaries of each of the five hypothesized regions (Talairach and Tournoux, 1988; Lancaster et al., 2000), as implemented in AFNI. For the second brain image in each panel, all colored areas showed a Valence main effect for the voxel-wise Period × Valence ANOVA ($P < 0.05$, corrected; Table 1 and Supplementary Table 1). Blue areas also showed greater activation for aversive than neutral trials during the anticipation period but not the picture period (aversive–neutral contrasts as indicated by corresponding voxel-wise t tests, $P < 0.05$, corrected; Supplementary Tables 4 and 5). In contrast, purple areas also showed greater activation for aversive than neutral trials during the picture period but not the anticipation period (aversive–neutral contrasts, as noted above). Yellow areas showed greater activation for aversive than neutral trials for the Valence effect and for the aversive–neutral contrast for each period, whereas green areas for the Valence main effect did not meet the $P < 0.05$ (corrected) threshold for either period. The view of the brain shown in each panel is indicated by the relevant Talairach coordinate. Time series plots of the circled clusters illustrate average percentage signal change across all time points of the aversive (red) and neutral (blue) trials. The onset of the 1-s picture presentation (P) occurred 3 s after warning cue (W) onset on half of the trials and 5 s after cue onset on the other half. Bar graphs of the circled clusters illustrate average percentage signal change for the anticipation period and picture period separately. Error bars for time series plots and bar graphs are for confidence intervals (Cumming and Finch, 2005) around the mean after adjusting for between-subject variance (Loftus and Masson, 1994). R = right. L = left.

Average percentage signal change values from the dilated cluster on the same and homologous side were extracted, and the values entered into appropriate repeated-measures MANOVAs (Keselman, 1998) with Hemisphere (Left, Right) as a within-subjects factor. The same procedure was used to test laterality for activated clusters in the other four a priori areas that were significant in either the right or left hemisphere. Smaller dilations resulted in very similar findings for laterality.

To assess relations between the right DLPFC and withdrawal-related unpleasant affect (Davidson, 2002; Nitschke and Heller, 2002) and between the OFC and both pleasant and unpleasant affect (Rolls, 1999; Nitschke et al., 2004), areas activated by aversive stimuli were correlated with the Negative Affect and Positive Affect scales of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). Pertinent to study hypotheses, the Negative Affect scale is comprised of 10 items that primarily index withdrawal-related unpleasant emotions (e.g., upset, distressed, scared). Subjects rated their current moods (state affect) on these scales while on the scanner bed immediately prior to the start of scanning and again immediately following the final functional scan. Because the findings for the two sets of state affect ratings were highly similar, results are reported for the average of the two. In addition, subjects rated their moods in general (trait affect) on these scales outside the scan room at the end of the experiment. One subject had missing data for the state form following the functional scans, and another had missing data for the trait form. Thus, they were not included in the corresponding correlational analyses for the right DLPFC or OFC.

Results

A conjunction analysis of the effects for the anticipation and picture periods tested our primary hypothesis that anticipation of aversive pictures as well as exposure to them would activate the amygdala, insula, ACC, right DLPFC, and OFC. Confirmatory results were found for the bilateral dorsal amygdala, bilateral anterior insula, dorsal ACC, right DLPFC, and right posterior OFC (Fig. 2; Table 1). The less stringent conjunction analysis method implemented in SPM99 and SPM2 (Friston et al., 1999a,b) resulted in the same effects although the clusters were substantially larger than found for the method used here. The more conservative approach to conjunction analysis recently proposed (Nichols et al., 2005; see also Friston et al., 2005) showed similar effects with the cluster sizes uniformly smaller for the hypothesized areas.

The Valence main effect for the Period × Valence voxel-wise ANOVA provided corroborating evidence for the aforementioned results of the conjunction analysis. Similar sectors of each of the five hypothesized regions showed greater activation for aversive than neutral trials (Fig. 2; Table 1). Post hoc *t* tests comparing aversive and neutral conditions for the anticipation and picture response periods separately revealed significant differences for all regions for picture anticipation at $P < 0.001$ and for picture exposure at $P < 0.006$. No clusters showed more activation during neutral than aversive trials.

To test whether any subregions of the five areas under investigation here activated during the anticipation of aversive pictures but not in response to them, we examined the Period × Valence interaction for the whole-brain, voxel-wise ANOVA. Of the five hypothesized brain areas, clusters in the rostral ACC, right DLPFC, and bilateral OFC showed this effect (Fig. 3; Table 1). The right OFC cluster (364 mm^3) was marginally significant ($P < 0.06$, corrected) and medial to the right OFC activation for the conjunction analysis and Valence main effect above. Post hoc *t* tests indicated that these ACC, DLPFC, and OFC regions showed more activation to aversive than neutral warning cues. In addition, all those regions except one of the two right rostral ACC clusters showed less activation to aversive than neutral pictures (all Ps < 0.05). There were no Period × Valence clusters in the five a priori brain areas that showed the converse pattern of more activation to aversive than neutral pictures (see Supplementary Note for ancillary analyses regarding the Period × Valence effects).

None of the activated areas identified in the conjunction analysis and ANOVA showed sex differences, as indicated by Sex × Period × Valence repeated-measures MANOVAs (see Materials and methods). The Sex × Valence and the Sex × Period × Valence interaction effects were not significant for any of the activations listed in Table 1. As shown in Figs. 2 and 3, a number of activated areas outside the five hypothesized regions showed a Valence main effect and the Period × Valence interaction (Supplementary Tables 1 and 2). Supplementary Tables 3–6 provide results for the Period main effect, voxel-wise *t* tests for the anticipation and picture periods separately, and ANOVAs and *t* tests for anatomically defined regions of interest.

To assess lateralization, each unilateral cluster of relevance to study hypotheses for the above conjunction analysis and ANOVAs was dilated and used to identify the homologous cluster in the

Table 1
Brain regions showing greater activation for aversive than neutral trials

Brain region (Brodmann areas)	Talairach coordinates			Size (mm^3)	*F* value
	x	y	z		
Conjunction analysis					
Dorsal ACC (32/24)	2	24	25	3274	
R DLPFC (10/9)	33	46	19	672	
R DLPFC (9)	41	15	28	1786	
R OFC (11/47)	26	32	−11	675	
R insula (13)	38	20	0	4310	
L insula (13)	−35	17	−1	4762	
R amygdala	16	−7	−11	871	
L amygdala	−20	−5	−13	704	
ANOVA valence main effect					
Rostral ACC (32)	5	46	8	2957	16.595
Dorsal ACC (32/24)	−4	21	32	4162	17.74
R DLPFC (10/9)	32	46	22	837	14.584
R DLPFC (9)	41	10	28	3022	17.201
R OFC (11/47)	26	35	−11	511	15.290
R insula (13)	41	14	3	4525	16.884
L insula (13)	−40	17	3	4704	17.194
R amygdala	18	−7	−9	1026	17.215
L amygdala	−18	−7	−12	840	19.677
ANOVA Period × Valence interaction effect					
Rostral ACC (32/24)	6	42	6	1302	13.563
Rostral ACC (24/32)	−16	42	3	792	15.061
R DLPFC (8/9)	40	27	43	564	15.018
R OFC (11)	16	41	−4	364	11.814
L OFC (11/47)	−22	40	−5	640	13.102

Results for conjunction analysis and the Valence main effect and interaction effect for voxel-wise Period × Valence ANOVA. *F* values for ANOVA effects are for the entire cluster. R = right. L = left. ACC = anterior cingulate cortex. DLPFC = dorsolateral prefrontal cortex. OFC = orbitofrontal cortex.

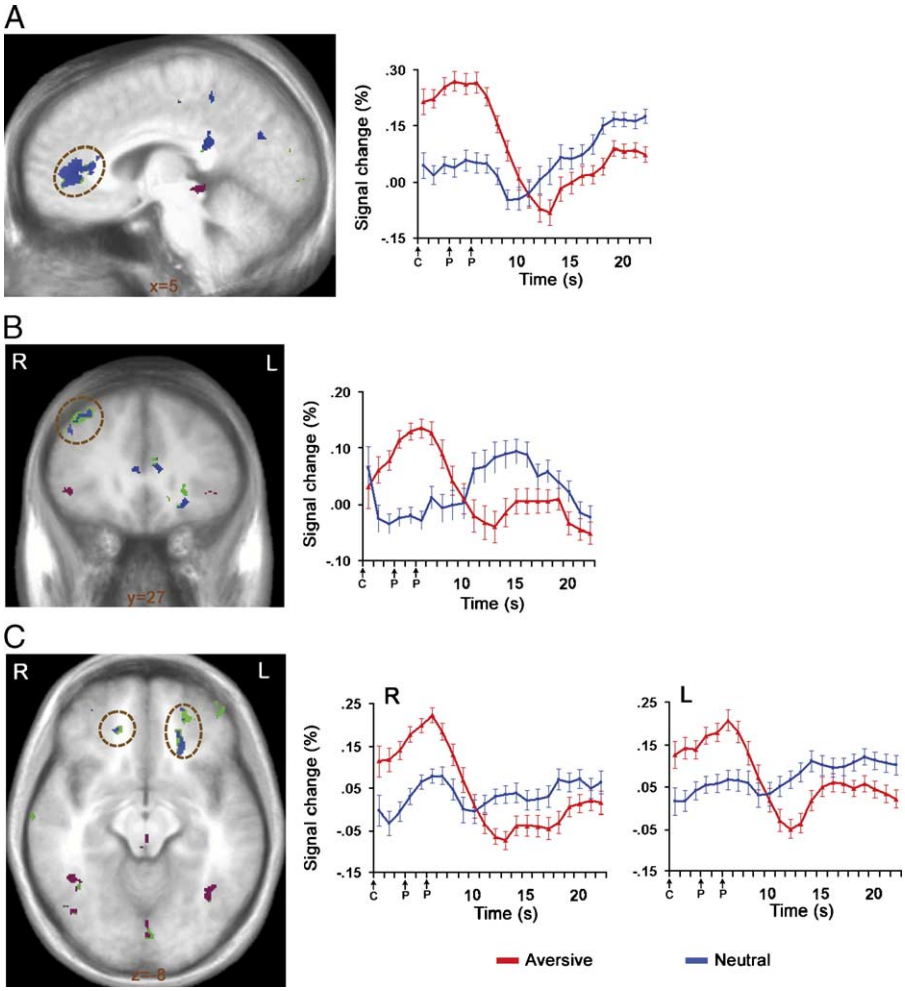


Fig. 3. Activations during the anticipation of aversion. The figure illustrates greater activation for aversive than neutral trials exclusively during the anticipation period in (A) rostral anterior cingulate cortex, (B) right dorsolateral prefrontal cortex, and (C) bilateral orbitofrontal cortex. All colored areas showed an interaction effect for the voxel-wise Period × Valence ANOVA ($P < 0.05$, corrected; Table 1 and Supplementary Table 2). Blue areas also showed greater activation for aversive than neutral trials during the anticipation period but not the picture period (aversive–neutral contrasts as indicated by corresponding voxel-wise t tests, $P < 0.05$, corrected; Supplementary Tables 4 and 5). In contrast, purple areas also showed greater activation for aversive than neutral trials during the picture period but not the anticipation period (aversive–neutral contrasts, as noted above). Green areas for the Valence main effect did not meet the $P < 0.05$ (corrected) threshold for the aversive–neutral contrast for either period. The view of the brain shown in each panel is indicated by the relevant Talairach coordinate. Time series plots of the circled clusters illustrate average percentage signal change across all time points of the aversive (red) and neutral (blue) trials. The onset of the 1-s picture presentation (P) occurred 3 s after warning cue (W) onset on half of the trials and 5 s after cue onset on the other half. Error bars are for confidence intervals (Cumming and Finch, 2005) around the mean after adjusting for between-subject variance (Loftus and Masson, 1994). R = right. L = left.

opposite hemisphere (see Materials and methods). Values of the resulting clusters were submitted to corresponding Period × Valence × Hemisphere MANOVAs. The two right DLPFC clusters identified by the conjunction analysis (Table 1) were asymmetric, as indicated by a Valence × Hemisphere interaction, BA 10/9, $F(1, 20) = 18.98$, $P < 0.001$, and BA 9, $F(1, 20) = 12.02$, $P = 0.002$. The highly similar two right DLPFC clusters for the Valence main effect of the voxel-wise Period × Valence ANOVA were also asymmetric, BA 10/9, $F(1, 20) = 18.12$, $P < 0.001$, and BA 9, $F(1, 20) = 17.87$, $P < 0.001$. For the Period × Valence interaction, the right DLPFC (BA 8/9) cluster was also lateralized, $F(1, 20) = 23.00$, $P < 0.001$. Asymmetries were found for the right OFC clusters for the conjunction analysis, $F(1, 20) = 23.53$, $P < 0.001$, and Valence main effect, $F(1, 20) = 5.06$, $P = 0.03$. Conversely, the OFC activations for the Period × Valence interaction were bilateral, as indicated by a nonsignificant Period × Valence × Hemisphere interaction. No amygdala or insula clusters were lateralized.

The association of right DLPFC and withdrawal-related unpleasant affect (Davidson, 2002; Nitschke and Heller, 2002) was tested by correlating right DLFPC activations in Table 1 (conjunction analysis and ANOVA results) and negative affect scores on the PANAS. Correlations were computed for the anticipation and picture periods separately. For all five right DLPFC clusters in Table 1, greater activation during the anticipation period on aversive than neutral trials was correlated with negative affect (Fig. 4). This pattern was most pronounced for the anterior right DLPFC cluster showing the Valence main effect in Fig. 2D. The anticipation period correlations with state ($r = 0.71$, $P < 0.001$) and trait ($r = 0.67$, $P = 0.001$) negative affect were significantly greater than the picture period correlations with state ($r = -0.23$, $P = 0.34$) and trait ($r = -0.27$, $P = 0.25$) negative

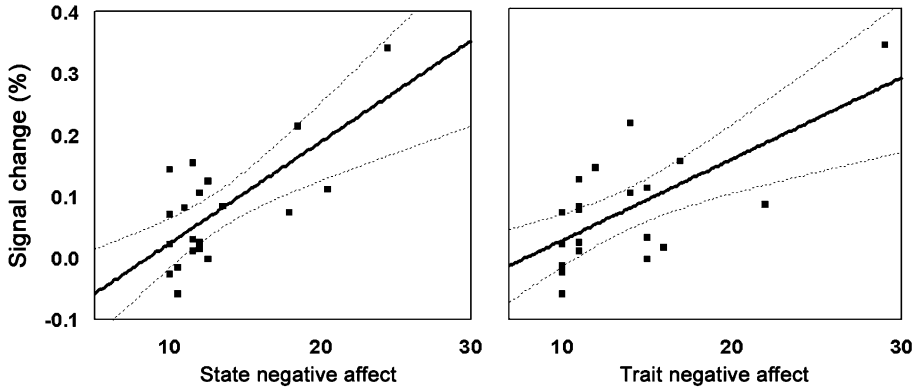


Fig. 4. Scatter plot showing the positive relationship between negative affect and right dorsolateral prefrontal cortex activation during the anticipation of aversive pictures. Plots illustrate the relationship of greater activation for aversive than neutral trials during the anticipation period in the right dorsolateral prefrontal area depicted in Fig. 2D to increases in (A) state negative affect ($r = 0.71$, $P < 0.001$) and (B) trait negative affect ($r = 0.67$, $P < 0.001$), as measured by the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). R = right. L = left.

affect ($t(17) = 2.90$, $P = 0.005$, and $t(17) = 2.84$, $P = 0.006$, respectively). Those anticipation period correlations were also of greater magnitude than anticipation period correlations with state ($r = 0.10$, $P = 0.69$) and trait ($r = 0.34$, $P = 0.14$) positive affect scores on the PANAS ($t(17) = 2.30$, $P = 0.02$, and $t(17) = 1.66$, $P = 0.06$, respectively).

The hypothesized association between the OFC and affect was tested in the same manner by correlating the four OFC activations in Table 1 and both positive affect and negative affect scores on the PANAS. For all four OFC clusters, greater activation during the anticipation period on aversive than neutral trials was correlated with both positive and negative affect (Fig. 5). This

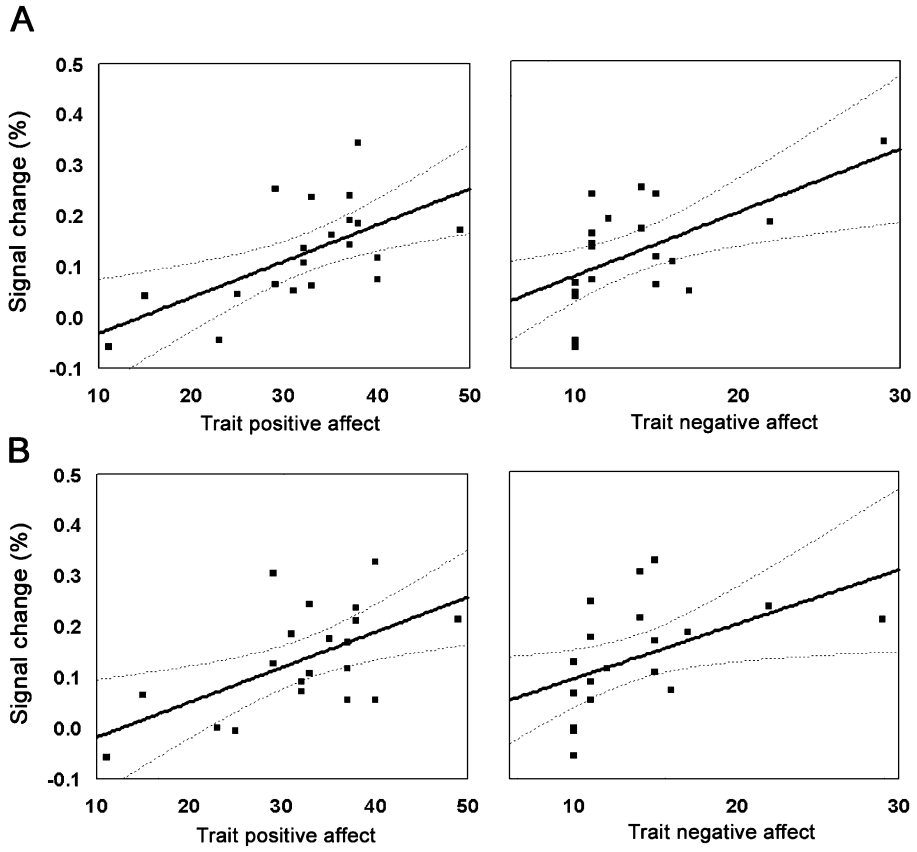


Fig. 5. Scatter plot showing the positive relationship between affect and bilateral orbitofrontal cortex activation during the anticipation of aversive pictures. (A) Plots illustrate the relationship of greater activation for aversive than neutral trials during the anticipation period in the left orbitofrontal area depicted in Fig. 3C to increases in trait positive affect ($r = 0.62$, $P = 0.004$) and trait negative affect ($r = 0.58$, $P = 0.007$), as measured by the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). (B) Plots illustrate the relationship of greater activation for aversive than neutral trials during the anticipation period in the right orbitofrontal area depicted in Fig. 3C to increases in trait positive affect ($r = 0.58$, $P = 0.007$) and trait negative affect ($r = 0.49$, $P = 0.03$), as measured by the PANAS. Correlations with state affect were of similar magnitude (rs ranging from 0.32 to 0.63).

pattern was most pronounced for the bilateral OFC clusters showing the Period × Valence interaction effect in Fig. 3C. For the left OFC, the anticipation period correlations with trait positive affect (r = 0.62, P = 0.004) and negative affect (r = 0.58, P = 0.007) were significantly greater than the picture period correlations with trait positive affect (r = −0.20, P = 0.40) and negative affect (r = 0.09, P = 0.69) ($t(17)$ = 3.64, P < 0.001, and $t(17)$ = 1.95, P = 0.03, respectively). The same pattern was observed for the right OFC: anticipation period correlations with trait positive affect (r = 0.58, P = 0.007) and negative affect (r = 0.49, P = 0.03) were significantly greater than the picture period correlations with trait positive affect (r = −0.26, P = 0.27) and negative affect (r = −0.06, P = 0.79) ($t(17)$ = 3.97, P < 0.001, and $t(17)$ = 2.12, P = 0.02, respectively). The correlations with state affect were highly similar.

Discussion

This study found that five key brain areas repeatedly implicated in previous research on aversion were activated not only when subjects viewed aversive visual stimuli but also in anticipation of them. The design of the rapid event-related fMRI paradigm, in tandem with advancing sophistication of data processing procedures, afforded the ability to delineate the respective contributions of the anticipation and picture periods to the hemodynamic responses elicited by aversion. Areas recruited both in anticipation of and in response to aversive pictures were the dorsal amygdala, anterior insula, dorsal ACC, right DLPFC, and posterior OFC. These findings are consistent with the idea that there is one system that governs both processes. In his seminal work on conditioning, Pavlov (1927) introduced this idea with his notion of stimulus substitution, stating that a warning signal comes to represent an aversive stimulus that follows it in conditioning trials because they both activate the same brain areas (pp. 36–38). More recently, LeDoux (2002) described aversive stimuli and warning signals that precede them as being served by a single brain system (pp. 6–7), providing a mechanistically detailed account for how this is accomplished in the amygdala. The anticipation of aversion is as integral to such aversive conditioning paradigms as it is to the paradigm featured in the present report.

Other sectors within the five hypothesized brain regions – the rostral ACC, a more superior sector of the right DLPFC, and more medial sectors of the OFC – activated more during anticipation of aversive pictures than in response to them. These findings suggest that anatomic distinctions within the ACC, right DLPFC, and OFC are important in distinguishing anticipatory and reactivity processes for aversive visual stimuli, as has been reported for other forms of aversion such as pain and taste (Ploghaus et al., 1999, 2003; O'Doherty et al., 2002; Wager et al., 2004). None of the five a priori areas activated more in response to aversive pictures than in anticipation of them.

Recruitment of the bilateral dorsal amygdala during aversive trials across anticipation and picture periods replicates findings reported in the literature for various forms of aversion (Büchel et al., 1998; LaBar et al., 1998; Davis and Whalen, 2001; LeDoux, 2002; Dalton et al., 2005). The amygdala results are also consistent with our previous startle reflex findings for a similar paradigm (Nitschke et al., 2002). A large corpus of work highlights the amygdala in the detection of aversion and more generally in vigilance for motivationally salient events (Davis, 1992; Davis and Whalen, 2001; LeDoux, 2002).

The co-activation of the insula and ACC found in the present study has been reported frequently in research on different forms of aversion (Chua et al., 1999; Ploghaus et al., 1999; Price, 2000; Phelps et al., 2001; Craig, 2002, 2003; Murphy et al., 2003; Wicker et al., 2003; Singer et al., 2004; Wager et al., 2004). These two regions are critical for the integration of sensory, affective, cognitive, autonomic, and motor processes (Augustine, 1996; Critchley et al., 2000, 2002b, 2003, 2004, 2005; Price, 2000; Singer et al., 2004). This integrative function is implemented via the extensive afferent and efferent projections of both areas (Augustine, 1996; Craig, 2002, 2003). Recent work indicates a related function of the insula in interoceptive awareness of aversion (Augustine, 1996; Phelps et al., 2001; Craig, 2002, 2003; Critchley et al., 2002a, 2004), including the representation of attendant autonomic responses (Yasui et al., 1991; Oppenheimer et al., 1992; Augustine, 1996; Phelps et al., 2001; Critchley et al., 2000, 2002a, 2004). The ACC, on the other hand, is particularly important for the generation of autonomic and behavioral responses (Tranel and Damasio, 1994; Mangina and Beuzeron-Mangina, 1996; Zahn et al., 1999; Critchley et al., 2002b, 2003). Studies employing the same standardized pictures used here have demonstrated robust skin conductance and cardiac responses to aversive pictures (Bradley et al., 2001). Concomitant recording of autonomic measures in future research with this event-related fMRI paradigm could begin to assess whether the insula and ACC activations found here serve the aforementioned roles in autonomic function.

The dorsal ACC activation to aversion observed across anticipation and picture periods was distinct from the rostral ACC region (i.e., pregenual sector of the ventral ACC) that showed greater activation to aversion during the anticipation than picture period. The rostral ACC findings are consistent with recent research on the anticipation of pain (Ploghaus et al., 2003). These separable ACC activations correspond well to anatomical and functional distinctions made in the literature between dorsal and ventral ACC (Devinsky et al., 1995; Bush et al., 2000; Davidson et al., 2002; Critchley, 2004; Nitschke and Mackiewicz, in press). The precise functions of these ACC sectors, particularly in relation to aversion, are not well established although recent proposals hold promise. Critchley posited that the afferent inputs from adjacent cortices determine which sector of the ACC signals the brainstem nuclei concerned with autonomic control. Another relevant perspective on ACC function is derived from research on response conflict (Cohen et al., 2000; Botvinick et al., 2004), with recent work emphasizing a dorsal/ventral distinction depending on the type of conflict (Davidson et al., 2002; Nitschke and Mackiewicz, in press). Future neuroimaging research manipulating response options and strategy utilization (Ochsner et al., 2002; Hertel, 1994) could further inform understanding of rostral and dorsal ACC function in the face of aversion.

The right DLPFC findings are in line with prior studies reporting right DLPFC activation in threat-related vigilance, withdrawal-related unpleasant emotion, and related psychopathology (Davidson, 2002; Nitschke and Heller, 2002). Right prefrontal activation has been observed in a wide array of research paradigms examining aversion, threat, and anxiety (Rauch et al., 1997; Kalin et al., 2000; Simpson et al., 2000; Rilling et al., 2001; Fischer et al., 2002; Dalton et al., 2005). In this study, we administered a well-validated self-report measure of negative affect indexing withdrawal-related unpleasant emotions. Individuals reporting elevated

negative affect showed greater activation in the right DLPFC during the anticipation of aversion than subjects reporting lower levels of negative affect. No association was observed between the right DLPFC and positive affect. The fact that the association with negative affect was observed in anticipation of aversive pictures and not in response to them indicates that anticipatory processes may figure importantly in previous demonstrations of associations between right DLPFC activation and withdrawal-related unpleasant affect.

Unique to the anticipation period, bilateral activations in homologous sectors of the OFC were medial to the right OFC activation observed across anticipation and picture periods. Numerous studies have implicated the OFC in both negative and positive emotion (Rauch et al., 1997; Rolls, 1999, 2004; Nitschke et al., 2004). Building on views of the OFC that emphasize the evaluation of affective stimuli (Rolls, 1999, 2004), we again found that OFC activation was associated with mood ratings for positive affect (Nitschke et al., 2004) as well as negative affect. As for the right DLPFC associations with negative affect, these OFC associations were observed for the anticipation of aversive pictures but not in response to them.

A limitation of the current design is the short interval between cue and picture presentation. As a result of the time course for the hemodynamic response being on the order of seconds, correlation between the two events is likely. Accordingly, we employed analytic procedures that ensured the maximal separation between the two events (see Materials and methods). Related to this limitation, anticipation in this paradigm may be accompanied by a tonic or increasing response across the anticipation period, which may result in anticipatory processes loading heavily on the regressor for the picture period thereby making activation during the anticipation period more difficult to detect. Differences in the intrinsic properties of the BOLD signal among brain areas might also result in heavier loadings for the picture period in one or more of the hypothesized brain areas. This bias toward activation in response to the picture may contribute to the results obtained for the Period main effect (Supplementary Table 3) where many regions showed greater activation for the picture period than the anticipation period and only one showed the converse pattern. Nonetheless, we observed robust responses for the anticipation of aversive pictures in all five brain areas investigated.

The formal assessment of lateralization in fMRI data is a recent development showcased in the present report, with asymmetries observed for the right DLPFC but not for the amygdala or insula, as predicted, and mixed evidence for the OFC. Future research could employ on-line ratings of mood in response to individual stimuli, based on previous work showing that certain DLPFC and OFC sectors index transient changes in affect (Ekman et al., 1990; Nitschke et al., 2004). To address the concern that the PANAS only assesses a circumscribed scope of affect (Larsen and Diener, 1992; Heller and Nitschke, 1998), the inclusion of additional items for assessing positive and negative affect did not alter correlations reported above for the right DLPFC and OFC.

In sum, the multiple nodes in the circuitry highlighted here contribute to the prediction and detection of aversion. Complementing the amygdala, insula, ACC, DLPFC, and OFC activations accompanying both anticipatory and reactivity processes, distinct sectors in the ACC, right DLPFC, and OFC were selectively activated during the anticipation of aversion. Preparation for impending aversive stimuli enhances one's ability to respond adaptively by recruiting some of the same resources that are eventually activated by the actual aversive event (Pavlov, 1927; LeDoux, 2002). Our data also indicate that negative mood is associated with right DLPFC activation when anticipating aversive events. Behavioral strategies for reducing anxiety might therefore most appropriately target anticipatory processes rather than affective responses to aversive stimuli. Affective disorders and excessive worry may well be more closely tied to anticipatory processes than is generally recognized, a hypothesis that should be examined in future research.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2005.06.068.

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