

Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study

Florin Dolcos,^{a,b,*} Kevin S. LaBar,^a and Roberto Cabeza^a

^aCenter for Cognitive Neuroscience, Duke University, Durham, NC 27708-0999, USA

^bCentre for Neuroscience, University of Alberta, Edmonton, AB, Canada, T6G 2S2

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Prefrontal cortex (PFC) activity associated with emotional evaluation and subsequent memory was investigated with event-related functional MRI (fMRI). Participants were scanned while rating the pleasantness of emotionally positive, negative, and neutral pictures, and memory for the pictures was tested after scanning. Emotional evaluation was measured by comparing activity during the picture rating task relative to baseline, and successful encoding was measured by comparing activity for subsequently remembered versus forgotten pictures (Dm effect). The effect of arousal on these measures was indicated by greater activity for both positive and negative pictures than for neutral ones, and the effect of valence was indicated by differences in activity between positive and negative pictures. The study yielded three main results. First, consistent with the valence hypothesis, specific regions in left dorsolateral PFC were more activated for positive than for negative picture evaluation, whereas regions in right ventrolateral PFC showed the converse pattern. Second, dorsomedial PFC activity was sensitive to emotional arousal, whereas ventromedial PFC activity was sensitive to positive valence, consistent with evidence linking these regions, respectively, to emotional processing and self-awareness or appetitive behavior. Finally, successful encoding (Dm) activity in left ventrolateral and dorsolateral PFC was greater for arousing than for neutral pictures. This finding suggests that the enhancing effect of emotion on memory formation is partly due to an augmentation of PFC-mediated strategic, semantic, and working memory operations. These results underscore the critical role of PFC in emotional evaluation and memory, and disentangle the effects of arousal and valence across PFC regions associated with different cognitive functions.

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Introduction

The domain of cognitive neuroscience of emotion has grown dramatically during the last decade. As a result of this develop-

ment, various effects of emotion on brain activation associated with different perceptual and cognitive functions have been revealed (reviewed in Davidson and Irwin, 1999; Lane and Nadel, 2000; Phan et al., 2002). To understand these diverse effects, researchers have often divided emotion into its basic underlying constructs. One dimensional approach to emotion emphasizes the contribution of two orthogonal components, namely *arousal* and *valence* (Lang et al., 1993; Russell, 1980). *Arousal* refers to a continuum that varies from calm to excitement, whereas *valence* refers to a continuum that varies from positive to negative with neutral in the middle (for methods to assess these two dimensions, see Bradley and Lang, 1994). The vast majority of studies has focused on the limbic system and particularly on the amygdala, whereas other components of the emotional processing network, such as the prefrontal cortex (PFC), have received relatively less attention. Recent studies of amygdala function have attempted to tease apart the relative contributions of the aforementioned affective dimensions to task performance (e.g., Anderson et al., 2003; Hamann et al., 2002; Phelps and Anderson, 1997; Phelps et al., 1998). However, the contribution of these factors to emotional processing in other frontolimbic regions is not well understood, and the available evidence is contradictory. To address this imbalance, the present functional MRI (fMRI) study focused on the role of PFC regions in emotional processing.

In particular, we investigated the effects of arousal and valence on emotional evaluation and emotional memory. Emotional evaluation refers to the perception and categorization of emotional stimuli, and emotional memory refers to the modulatory effect of emotion on different stages of memory processing, including encoding, consolidation, and retrieval. In the domain of emotional evaluation, the amygdala is assumed to be involved in the rapid detection of the basic emotional properties of incoming stimuli, whereas PFC is assumed to be involved in higher-order emotional evaluation processes, which operate in close interaction with other cognitive functions and with behavioral goals (Davidson and Irwin, 1999). In the domain of emotional memory, the existing studies have focused on the amygdala and identified arousal-mediated effects at encoding that predict subsequent memory (Cahill et al., 1996; Canli et al., 2000, 2002; Dolcos et al., 2003, 2004; Hamann et al., 1999), but there is little understanding of the contribution of other brain regions, such as PFC regions. Although it is assumed

* Corresponding author. Brain Imaging and Analysis Center, Room 163, Bell Building, PO Box 3918, Duke University, Durham, NC 27710. Fax: +1-919-681-7033.

E-mail address: fdolcos@duke.edu (F. Dolcos).

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that activation during emotional evaluation tasks plays a role in memory, few studies have explicitly examined the relationship between emotional evaluation and memory. Thus, the overarching goal of the present study was to carefully investigate the contribution of the PFC to arousal and valence effects on emotional evaluation and memory.

Different PFC subregions are likely to make distinct contributions to emotional evaluation, but information about this issue is scarce. A basic anatomical distinction in this domain is between lateral and medial PFC regions. According to one prevailing view, the role of lateral PFC regions in emotional evaluation is primarily related to valence. The valence hypothesis states that the left PFC is dominant in the processing of positive emotions, whereas the right PFC is dominant in the processing of negative emotions (Davidson, 1995; Davidson and Irwin, 1999). This hypothesis is inspired by evidence from lesion literature and is mainly supported by electrophysiological evidence from EEG recordings. Neuropsychological evidence shows that patients with left hemisphere lesions tend to experience negative emotions, such as sadness (Morris et al., 1996; Paradiso et al., 1999a), whereas patients with right hemisphere damage are biased toward experiencing positive emotions, such as euphoria (e.g., Starkstein et al., 1989). The results of some electrophysiological studies are consistent with the valence hypothesis and support the idea that this valence-related PFC lateralization may depend either on transiently induced affective states or on stable personality traits (Aftanas et al., 2001; Davidson, 1995; Davidson and Irwin, 1999; Tomarken et al., 1992; Wheeler et al., 1993).

However, electrophysiological studies do not provide an accurate localization of the sources of these valence effects, and, overall, the evidence supporting the valence hypothesis has been mixed. First, neither lesion nor electrophysiological evidence has always been consistent with the valence hypothesis (e.g., Borod, 1992; Borod et al., 1998; Dolcos and Cabeza, 2002; Hagemann et al., 1998). Second, functional neuroimaging evidence is also inconclusive. Whereas some studies support the valence hypothesis (e.g., Canli et al., 1998), some studies do not report valence-related hemispheric asymmetry in PFC (e.g., Baker et al., 1997; George et al., 1995; Lane et al., 1997a,b,c; Pardo et al., 1993; Teasdale et al., 1999). One possible reason why the results have been mixed is that arousal and valence are often not distinguished carefully (but see Canli et al., 1998); hence, valence effects might have been confounded with arousal effects. Thus, the first goal of the present study was to investigate the valence hypothesis and identify the specific PFC regions involved, in conditions where positive and negative stimuli were matched in arousal and other potentially confounding factors were controlled.

As for the role of medial PFC regions in emotional evaluation, different hypotheses have been suggested. For instance, orbitofrontal areas of medial PFC have been linked to the rewarding nature of stimuli (e.g., O'Doherty et al., 2001; Rolls, 2000), and anteromedial areas have been related to more personal and subjective aspects of experiencing internal states (e.g., Frith and Frith, 1999). Although medial PFC regions have been strongly associated with emotional processing, it is unclear whether the role of these regions is related to arousal or to valence. Given that medial PFC regions are systematically activated by emotional stimuli, regardless of their valence (for a review, see Phan et al., 2002), PFC involvement could be attributed to its role in the processing of arousal. This notion is consistent with evidence supporting medial PFC involvement in processing emotionally arousing stimuli

irrespective of valence (Lane et al., 1997a,b,c; Reiman, 1997; Reiman et al., 1997; Schneider et al., 1995; Teasdale et al., 1999). On the other hand, there is also evidence suggesting valence-related specificity in medial PFC (e.g., George et al., 1995; Paradiso et al., 1999b). In particular, medial PFC has been associated with affiliative behaviors and appetitive or reward circuits (e.g., Rolls, 2000). A recent metaanalysis of functional neuroimaging studies of emotion (Wager et al., 2003) found that, overall, medial PFC activity was associated with approach or appetitive tasks. To address this issue, the second goal of the present study was to determine whether the role of medial PFC in emotional processing is primarily related to arousal or to valence, or whether there are subregions within medial PFC differently involved in arousal and valence.

Turning to emotional memory, the most basic phenomenon to explain in this domain is why arousing events (both positive and negative) are better remembered than neutral events (Bradley et al., 1992; Christianson, 1992). This effect has been attributed to the modulatory effect of the amygdala on the medial temporal lobe (MTL) memory system (McGaugh et al., 2002), and this modulation hypothesis has been confirmed by functional neuroimaging studies (Cahill et al., 1996; Canli et al., 2000, 2002; Dolcos et al., 2003, 2004; Hamann et al., 1999; Kilpatrick and Cahill, 2003). For example, we investigated this hypothesis using event-related fMRI and the subsequent memory paradigm (Paller and Wagner, 2002). In this paradigm, memory performance on a subsequent memory task is used to sort encoding items into two categories: remembered versus forgotten. Greater encoding activity for remembered than forgotten items, sometimes known as “the Dm (difference in memory) effect”, is assumed to reflect successful encoding operations. Consistent with the modulation hypothesis, we found that the Dm effects in the amygdala and the MTL memory regions were greater for emotionally arousing pictures than for neutral pictures, and that the two Dm effects were more strongly correlated in the case of arousing pictures than in the case of neutral pictures (Dolcos et al., 2004).

Although this evidence strongly links the memory-enhancing effect of emotion to an MTL mechanism, it does not exclude the possibility that other brain regions, such as PFC, also play a major role. In fact, in functional neuroimaging studies, PFC regions are as strongly associated with successful encoding operations as MTL regions (e.g., Brewer et al., 1998; Paller and Wagner, 2002; Wagner et al., 1998). Also, the effects of several factors affecting encoding success, such as organizational strategies and attention, have been found to be mediated by changes in PFC activity (Anderson et al., 2000; Fletcher et al., 1998; Kensinger et al., 2003). Moreover, studies using transcranial magnetic stimulation (TMS) have shown that PFC activity is actually necessary for successful encoding (Epstein et al., 2002; Grafman and Wassermann, 1999; Rossi et al., 2001). Thus, it is quite likely that the enhancing effect of emotion on encoding is mediated not only by MTL but also by PFC. Yet, very little is known about the role of PFC on emotional memory formation (see, however, Canli et al., 2002; Kilpatrick and Cahill, 2003). For example, it is uncertain if the Dm effect in PFC is enhanced by emotion, similar to what we found in MTL (Dolcos et al., 2004). It is also unclear whether this putative effect is due to arousal or valence, and which specific PFC regions are involved. Thus, the third goal of the study was to investigate the role of PFC in the formation of emotional memory.

The method we employed has two main features: (1) it distinguishes between activity associated with emotional evalua-

tion and emotional memory, and (2) it distinguishes between the effects of arousal and valence. Participants were scanned while rating the pleasantness of arousing pictures (positive and negative) and non-arousing pictures (neutral), and after scanning, they recalled the contents of the pictures. Stimuli were selected from a standardized set of pictures that allows experimental control over arousal and valence characteristics (Lang et al., 1997), which has been largely used in neuroimaging studies of emotion (e.g., Dolan et al., 2000; Hamann et al., 1999, 2002; Lane et al., 1997a,b,c, 1999; Liberzon et al., 2000; Paradiso et al., 1999b; Taylor et al., 1998, 2000). Evaluation activity was measured by comparing activity during picture rating to the baseline activity, and successful encoding activity was measured by comparing activity for subsequently remembered versus subsequently forgotten pictures (Dm effect). Given that positive and negative pictures were both more arousing than neutral pictures, arousal effects should affect both positive and negative pictures. Given that positive and negative pictures were matched in arousal, differences between them should reflect valence effects rather than arousal effects. Thus, the effect of arousal was defined as greater activity for both positive and negative pictures than for neutral pictures, and the effect of valence, as differences between activity for positive and negative pictures.

To summarize, we investigated three main issues. First, we investigated the valence hypothesis, and in particular, what specific left and right PFC subregions would be sensitive to valence effects. Second, we investigated the role of medial PFC in emotional evaluation, and specifically, whether activity in this region is primarily sensitive to arousal or valence, or whether subregions can be distinguished. Finally, we investigated the role of PFC in emotional memory, and particularly, the relationship of Dm effects with stimulus arousal and valence, and their localization within PFC.

Methods

Subjects

Sixteen young (25 + 4.6 years), right-handed, healthy women participated in the study. Female participants were chosen because evidence suggests that they are more likely to display strong physiological responses to emotional stimuli (Lang et al., 1993) and report more intense emotional experiences (Shields, 1991) than men. All participants consented to a protocol approved by Duke University Institutional Review Board.

Materials

Stimuli consisted of 60 positive, 60 negative, and 60 neutral pictures selected from the International Affective Picture System (IAPS) picture database (Lang et al., 1997), on the basis of their normative arousal and valence scores. The mean arousal scores (1 = calm, 9 = excited) were 6.0 for positive (SD = 2.2), 6.15 for negative (SD = 2.2), and 3.15 for neutral pictures (SD = 2.0). Thus, positive and negative pictures had similar high arousal scores, whereas neutral pictures had low arousal scores. The mean valence scores (1 = negative, 5 = neutral, 9 = positive) were 7.1 for positive (SD = 1.7), 2.3 for negative (SD = 1.5), and 5.2 for neutral (SD = 1.4). To equate the emotional and neutral categories for visual complexity and content (e.g., human presence), the IAPS pictures were supplemented with neutral pictures from other sources (Yama-

saki et al., 2002). Also, given the evidence that dorsal–ventral PFC regions are differently involved in the processing of visual stimuli depending on their spatial content (e.g., Goldman-Rakic, 1995), it was important to determine that spatial/scene content did not differ between emotional and neutral stimuli. To investigate this idea, we asked 10 participants to rate our stimuli using a scene content scale (1 = no scene, 4 = very high scene content). The ratings for emotional (1.86) and neutral (1.93) pictures were similar ($T = 0.64$, $P > 0.5$), suggesting an equivalent amount of scene/spatial information across the stimulus categories.

Experimental design

The pool of 180 pictures was divided into six sets of 30 pictures (10 positive, 10 negative, and 10 neutral), which were randomly assigned to six study blocks. Six different block orders were randomly assigned to the participants. To avoid the induction of long-lasting mood states, the pictures within each block were pseudo-randomized so that no more than two pictures of the same valence were consecutively presented. Functional MR images were recorded while subjects viewed emotional and neutral pictures. The pictures were presented, using an LCD projector, to a screen located behind the subjects' crown that subjects could see via an angled mirror. Each picture was presented for 3 s and followed by a 12-s fixation cross. Participants were instructed to experience any feelings or thoughts the pictures might elicit in them, and to rate each picture in a 3-point pleasantness scale (1 = negative, 2 = neutral, 3 = positive). Rating the emotional valence of stimuli was employed because paying attention to emotional responses elicited by various stimuli is associated with deep encoding, which results in better subsequent memory performance. This task also provides an estimation of subjects' emotional responses. Nothing was mentioned about a subsequent memory test, before or during the encoding task, and hence learning was incidental. Incidental learning was preferred because intentional learning may interfere with the experience of emotions, and because differences in voluntary attention may complicate the interpretation of subsequent memory effects.

Forty-five minutes after the scanning session, subjects performed an unexpected cued-recall test conducted outside the MRI suite. Subjects were provided with one- or two-word written cues for each picture (e.g., snake, building, skydivers), and had to describe in writing, and in as much detail as they could, the pictures that they remembered. Similar to the procedure employed in our previous ERP study (Dolcos and Cabeza, 2002), participants were asked to provide enough relevant details (e.g., about the number of elements, color, action, etc.) so that an outsider could identify each picture and discriminate it from similar studied pictures (e.g., a brown snake facing viewer vs. several small green snakes). The test lasted until participants could not recall any additional pictures or until a maximum of 50 min had elapsed. Two raters were involved in scoring participants' responses, and only those pictures whose description was detailed enough to allow both identification and discrimination were classified as remembered.

MRI data acquisition

Anatomical scanning

Neuroimaging was performed using a 1.5 T GE scanner. A T1-weighted sagittal localizer series was first acquired. The anterior (AC) and posterior commissures (PC) were identified in the

midsagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms TR (repetition time), a 9-ms TE (echo time), a 24-cm FOV (field of view), a 256^2 matrix, and a slice thickness of 3.75 mm. A second series of 46 oblique T1-weighted images perpendicular to the AC-PC was then acquired using the same imaging parameters.

Functional scanning

Thirty-four contiguous gradient-echo echoplanar images (EPIs) sensitive to blood oxygen level dependent (BOLD) contrast were acquired parallel to the AC-PC plane, using the same slice prescription described above for the near-axial structural images. The EPIs were acquired with a 3-s TR, 40-ms TE, one radio frequency excitation, 24-cm FOV, 64^2 image matrix, and a 90° flip angle. Slice thickness was 3.75 mm, resulting in cubic 3.75 mm^3 isotropic voxels.

fMRI data analysis

Image preprocessing

Image preprocessing and statistical analyses were performed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm/>). Functional images were corrected for acquisition order and realigned to correct for motion artifacts. Anatomical images were coregistered with the first functional images for each subject, and then both anatomical and functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM99. Subsequently, functional images were spatially smoothed using an 8-mm isotropic Gaussian kernel.

Statistical analyses

Statistical analyses were separately performed to assess both emotion-related (emotional evaluation) and memory-related differences (emotional encoding) between emotional and neutral pictures. The images were defined as unpleasant, neutral, or pleasant based on the IAPS ratings. The use of the IAPS score was justified by two reasons. First, different from the rating scores, which due to technical limitations during scanning (i.e., the response box had only three response options) did not allow fine evaluations of the subjects' emotional response, the IAPS scores are based on more sophisticated methods of assessing emotional arousal and valence, and allow much finer dissociations. Second, although some subjects classified some of the images differently than the norms, the high correlation between the average picture scores as rated by the subjects and the IAPS valence scores ($R = 0.9$, $P < 0.0001$) suggest that participants' classification was highly consistent with the normative data. Therefore, the latter scores were used to dissociate the effect of arousal and valence on brain activity associated with emotional evaluation and emotional memory formation. For each subject, task-related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response (HDR) and its temporal derivative. The general linear model, as implemented in SPM99, was used to model the effects of interest and other confounding effects (e.g., session effects and magnetic field drift). Functional images were proportionally scaled to the whole-brain signal.

Group analyses were conducted using random-effects models to assess the effect of arousal and valence on emotional evaluation and emotional encoding. In the present manuscript, we report the PFC

results, with a focus on lateral and medial cortices, excepting motor and cingulate regions. The MTL results were reported in different manuscripts (Dolcos et al., 2003, 2004). Conjunction analyses were used to identify brain regions more activated in two conditions (e.g., positive and negative) than in a third condition (e.g., neutral). This was done using the ImCalc feature in SPM, and according to the following formula: $[(\text{Condition 1 } T \text{ score} > 2.01) \times (\text{Condition 2 } T \text{ score} > 2.01)]$. This procedure yields a mask containing only those voxels that were significantly activated above $T = 2.01$ ($P = 0.0316$) in each and both contrasts. 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: $0.0316 \times 0.0316 = P < 0.001$ (e.g., Allan et al., 2000; Cabeza et al., 2002).

The resulting conjunction masks provided information about the extent of the overlapping activations associated with the conditions involved in the conjunction, but not about the intensity of the overlapping activity. For this, conjunction T maps were calculated by multiplying the T values for the conditions of interest in the overlapping regions. The conjunction T maps were calculated according to the following formula: $[(\text{Condition 1 } T \text{ score}) \times (\text{Condition 2 } T \text{ score}) \times (\text{Conjunction mask of Condition 1 and Condition 2})]$. These are the T values we report.

For emotional evaluation, the effect of arousal was measured as greater activity (compared to baseline) for arousing stimuli (positive and negative pictures) than for non-arousing stimuli (neutral pictures). This was done by identifying regions that showed *both* (1) greater activity for positive than for neutral pictures, and (2) greater activity for negative than for neutral pictures. That is, the *effect of arousal on emotional evaluation* was defined as $[(\text{positive} > \text{neutral}) \text{ conj } (\text{negative} > \text{neutral})]$. The effect of valence was measured as significant differences between positive and negative pictures. Since the valence scales had neutral as an intermediate value between positive and negative, we further required that regions associated with positive or negative valence had to be more activated in these conditions than in the neutral condition. That is, the *effect of positive valence on emotional evaluation* was defined as $[(\text{positive} > \text{neutral}) \text{ conj } (\text{positive} > \text{neutral})]$ and the *effect of negative valence on emotional evaluation* was defined as $[(\text{negative} > \text{positive}) \text{ conj } (\text{negative} > \text{neutral})]$.

The same kind of analyses were performed for emotional encoding, except that instead of using activity during picture rating compared to baseline, we used differences in activity between remembered and forgotten items ($Dm = \text{activity for remembered pictures} - \text{activity for forgotten pictures}$). Dm activity was separately calculated for each picture category (e.g., $Dm \text{ positive} = \text{positive remembered} - \text{positive forgotten}$), and then the effects of arousal and valence were identified by comparing the three types of Dm activity. The *effect of arousal on emotional memory* was defined as $[(Dm \text{ positive} > Dm \text{ neutral}) \text{ conj } (Dm \text{ negative} > Dm \text{ neutral})]$. The *effect of positive valence on emotional memory* was defined as $[(Dm \text{ positive} > Dm \text{ negative}) \text{ conj } (Dm \text{ positive} > Dm \text{ neutral})]$ and the *effect of negative valence on emotional memory* was defined as $[(Dm \text{ negative} > Dm \text{ positive}) \text{ conj } (Dm \text{ negative} > Dm \text{ neutral})]$. To make sure that the differences between Dms occurred due to positive activations in the condition of interest and were not driven by deactivations in the other conditions, the conjunction maps were inclusively masked with the activation maps showing the main effect of memory (Dm) for the condition of interest at $P < 0.05$. For instance, for the latter comparison (i.e.,

[(Dm negative > Dm positive) conj (Dm negative > Dm neutral)], the resulting map was masked with the activation map for Dm negative. Thus, the final conjunction map contained only the voxels that showed a significant Dm for negative pictures.

The bar graphs of fMRI activations were examined by extracting the mean effect size from the peak voxel of each region, as identified by the SPM conjunction analyses for each condition of interest and subject. The data extraction was accomplished using SPM99. The *xyz* coordinates provided by SPM, which are in Montreal Neurological Institute (MNI) brain space, were converted to *xyz* coordinates in Talairach and Tournoux's brain space (Talairach and Tournoux, 1988).

Results

Behavioral results

Valence ratings

The average valence scores (1 = negative, 2 = neutral, 3 = positive) as rated by the participants in the scanner were 1.14 (SD = 0.16) for negative pictures, 2.18 (SD = 0.40) for neutral pictures, and 2.64 (SD = 0.26) for positive pictures. All pairwise comparisons were significant ($P < 0.0001$). Thus, the subjects' rating scores were consistent with those provided in the IAPS norms (Lang et al., 1997). Further validating this consistency, the correlation between our subjects' average scores and the normed IAPS scores of the pictures used in the present study was highly significant ($R = 0.90$, $P < 0.0001$).

Memory performance

Arousing pictures, both positive and negative, were better recalled than neutral pictures. Out of 60 pictures per category, participants recalled an average of 52% positive, 53% negative, and 38% neutral pictures (SDs were 4.5, 4.8, and 4.8, respectively). An ANOVA yielded a significant picture type effect ($F(2,15) = 41.21$, $P < 0.0001$), and post-hoc contrasts showed that recall of positive and negative pictures was similar ($P > 0.05$), and greater than recall of neutral pictures ($P < 0.0001$).

fMRI results

The analyses on activity associated with emotional evaluation (rating-baseline) yielded dissociable PFC regions showing effects of arousal and valence. In lateral PFC, the main goal was to test the valence hypothesis. Consistent with this hypothesis, a valence-related hemispheric asymmetry was found: a left dorsolateral PFC region (BA 8/9; *xyz* = -41, 21, 48; $T = 8.63$) showed an effect of positive valence, whereas a right ventrolateral PFC region (BA 47; *xyz* = 49, 33, -2; $T = 17.03$) showed an effect of negative valence. As illustrated by Fig. 1, the left PFC region was more activated for positive than for negative pictures, whereas the right PFC region was more activated for negative than for positive pictures. However, this asymmetry was not present in the entire lateral PFC: other dorsolateral PFC areas (BA 9) showed a bilateral (*xyz* = 49, 9, 24/-38, 9, 24; $T = 20.02/T = 15.41$) effect of negative valence. The effect of arousal in lateral PFC was evident in an area of the right inferior frontal gyrus (BA 47; *xyz* = 30, 18, -17; $T = 9.57$).

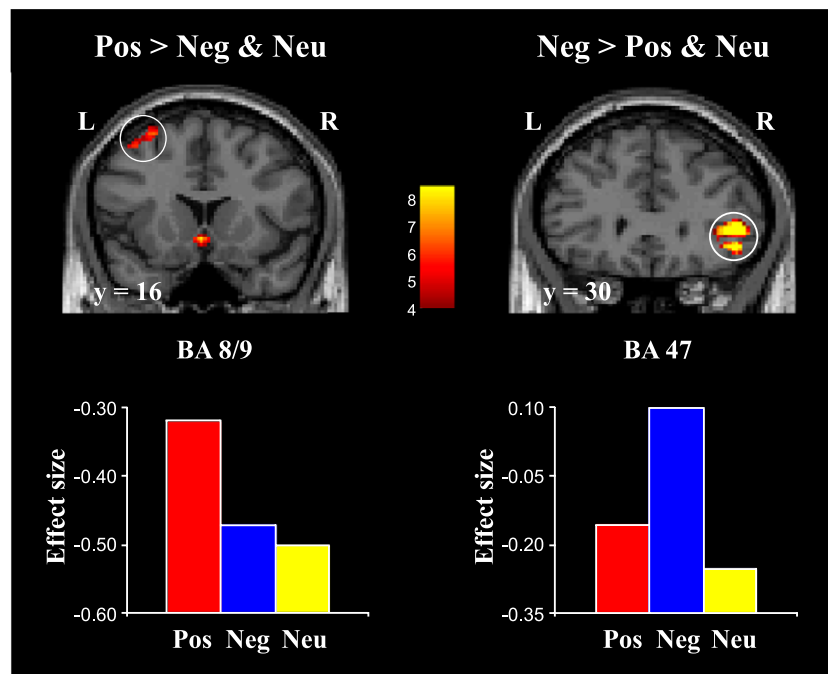


Fig. 1. Activity in lateral PFC showed evidence for the valence hypothesis. In the left hemisphere, a dorsolateral PFC region (BA 8/9) was more activated during evaluation of positive pictures than during evaluation of negative pictures, whereas in the right hemisphere, ventrolateral regions (BA 47) were more activated for negative than for positive pictures. The upper panels show the activation maps overlapped on high-resolution coronal anatomical images, and the bar graphs at the bottom show the effect size as extracted from the peak-voxels identified in the conjunction analyses (see Methods). The numbers at the left-bottom corner of the upper panels (e.g., $y = 16$) indicate the coordinate in MNI space. The color bar located between the upper panels indicates the conjunction T values. L = left, R = right; Pos = positive, Neg = negative, Neu = neutral; BA = Brodmann Area.

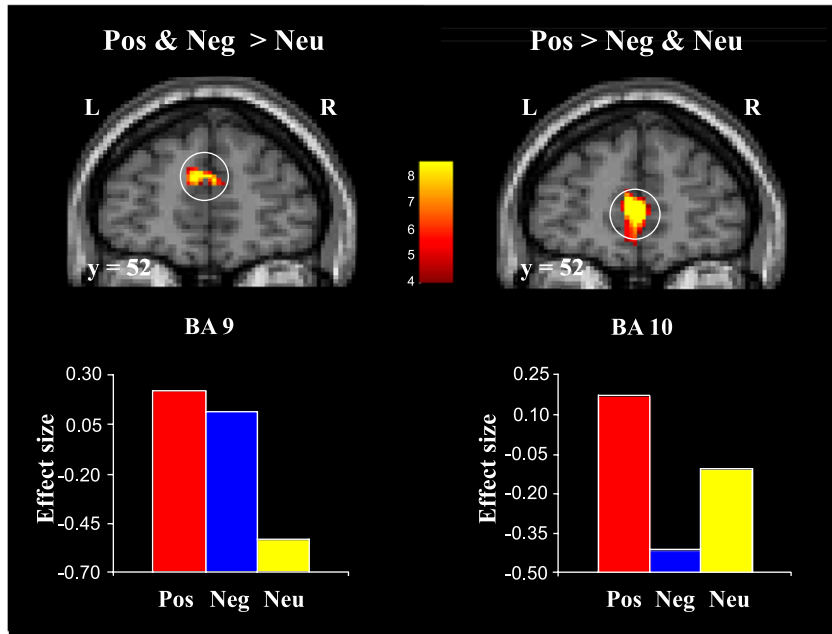


Fig. 2. Activity in medial PFC identified dissociable regions associated with arousal and positive valence. Dorsomedial PFC (BA 9) activity was sensitive to arousal (Pos and Neg > Neu), whereas ventromedial PFC (BA 10) activity was sensitive to positive valence (Pos > Neg and Neu). L = left, R = right; Pos = positive, Neg = negative, Neu = neutral; BA = Brodmann Area.

In medial PFC, a dorsal–ventral distinction was found during emotional evaluation in which arousal effects were in a dorsal region (BA 9; $xyz = -4, 52, 19$; $T = 11.45$), whereas valence effects were found in more ventral locations—orbitofrontal and antero-medial cortices (BA 10; $xyz = 0, 58, -10/0, 58, 4$; $T = 14.72/T = 30.2$). As illustrated by Fig. 2, the dorsomedial PFC region was

more activated during evaluation of both pleasant and unpleasant pictures than during evaluation of neutral pictures, whereas the ventral regions were more activated during the evaluation of positive pictures.

The analysis of activity associated with emotional memory (Dm = remembered – forgotten) also yielded PFC regions

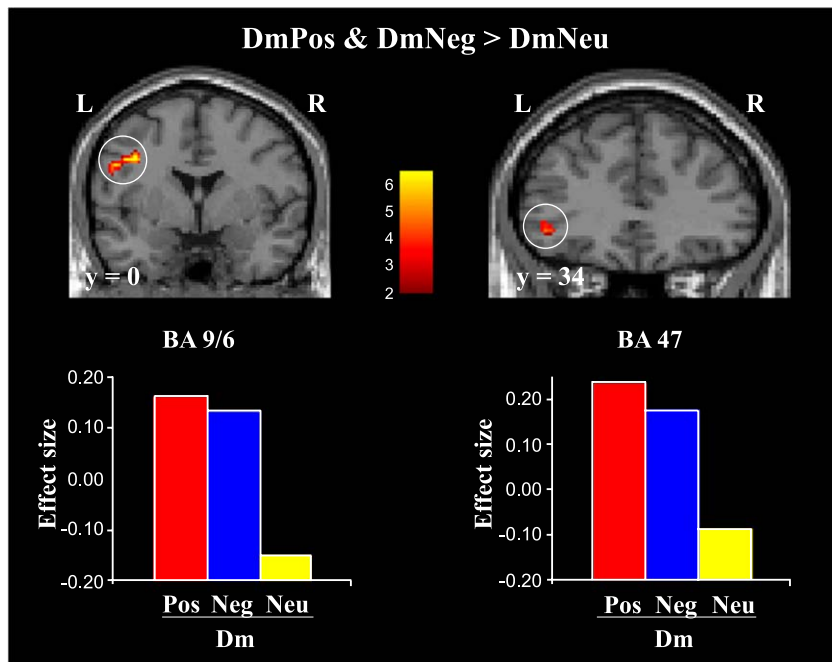


Fig. 3. Arousal enhanced successful encoding activity (Dm) in left PFC. Compared to the Dm for neutral pictures, the Dm for arousing pictures (both positive and negative) was greater in left ventrolateral (BA 47) and dorsolateral (BA 9/6) PFC regions. L = left, R = right; Pos = positive, Neg = negative, Neu = neutral; BA = Brodmann Area; Dm = remembered – forgotten.

showing effects of arousal and valence. The areas showing effects of arousal were found only in the lateral PFC, and included both ventral (BA 47; $xyz = -49, 29, -1$; $T = 5.48$) and dorsal (BA 9/6; $xyz = -38, 2, 31$; $T = 8.64$) locations. As illustrated by Fig. 3, in these lateral PFC regions, the Dm for positive pictures and the Dm for negative pictures were both greater than the Dm for neutral pictures. The average effect size values for remembered and forgotten pleasant, unpleasant, and neutral items, respectively, are as follows: BA 47 ($-0.22, -0.46, -0.13, -0.30, -0.31$, and -0.22) and BA 9/6 ($-0.24, -0.41, -0.09, -0.22, -0.31$, and -0.16). The areas showing effects of valence included medial (BA 9; $xyz = -11, 38, 29$; $T = 6.41$) and lateral (BA 45; $xyz = -49, 22, 3$; $T = 8.51$) locations, both showing an effect of positive valence.

Discussion

The present study yielded three main findings relevant for understanding PFC contributions to emotional evaluation and memory. First, consistent with the valence hypothesis, during emotional evaluation, specific left dorsolateral PFC areas showed greater activity for positive than for negative pictures, whereas right ventrolateral PFC areas showed the converse pattern. Second, also during emotional evaluation, dorsomedial PFC activity was sensitive to arousal (greater activation for both positive and negative pictures relative to neutral ones), whereas ventromedial PFC activity was sensitive to valence (greater activation for positive pictures relative to negative ones). Finally, demonstrating the role of lateral PFC in emotional memory, arousal enhanced successful encoding activity in left ventrolateral and dorsolateral PFC. These results provide evidence for multiple, regionally specific emotional influences on PFC function. The implications of the findings are discussed in separate sections below.

Lateral PFC showed a hemispheric asymmetry consistent with the valence hypothesis

As illustrated by Fig. 1, a left PFC region was more activated for positive than for negative pictures and a right PFC region showed the converse pattern. This finding is consistent with other evidence supporting the valence hypothesis (Aftanas et al., 2001; Canli et al., 1998; Davidson, 1995; Tomarken et al., 1992; Wheeler et al., 1993), but it extends this evidence in two ways.

First, the present finding demonstrates hemispheric asymmetry effects predicted by the valence hypothesis under conditions in which positive and negative stimuli were matched for arousal and visual properties, and in which the effects of valence could be distinguished from the effects of arousal on a trial-by-trial basis. As noted before (see Methods), positive and negative stimuli had similar normative scores of arousal and were equivalent in terms of complexity, presence of human figures, and other lower-level visual features. Participant ratings obtained on-line during encoding confirmed the valence manipulation and were highly correlated with normative valence scores. Moreover, the inclusion of neutral pictures allowed us to disentangle valence effects from arousal effects. Since arousal effects are by definition common to positive and negative pictures, these effects should appear as greater activity for both positive and negative pictures than for neutral pictures. As illustrated by Fig. 1, this was not the case in either the left or the right PFC regions comprising valence-related hemispheric asymmetry. Additionally, in contrast to previous findings

(Canli et al., 1998), which could not determine whether hemispheric asymmetries were stimulus-specific or reflected sustained changes in affective states, the present study provides evidence supporting the valence hypothesis using an event-related design in which stimuli were randomized during scanning.

Second, the present results not only demonstrated a valence-related hemispheric asymmetry but also identified the specific left and right PFC regions associated with positive and negative valence. The valence hypothesis has been primarily supported using electrophysiological methods (Aftanas et al., 2001; Davidson, 1995; Tomarken et al., 1992; Wheeler et al., 1993), which do not allow a good localization of neural sources. Evidence for the valence hypothesis was also found using fMRI (Canli et al., 1998) but using analyses that collapsed activity over a whole hemisphere. In contrast, the present result shows that the left PFC region specifically sensitive to positive valence is in dorsolateral cortex (middle frontal gyrus; BA 8/9) whereas the right PFC region particularly sensitive to negative valence is in ventrolateral cortex (inferior frontal gyrus; BA 47). A more inferior sector of BA9, in contrast, did not show such asymmetry effects, and was sensitive to negative valence bilaterally.

What are the implications of this region-specific hemispheric asymmetry in the processing of emotional valence? As described above, lesion, electrophysiological, as well as the available neuroimaging evidence supporting the valence hypothesis lacks the regional specificity necessary to link activity in the regions identified here with possible differential involvement in processing emotional valence. One possibility is to broadly explain the role of these regions based on the available neuroimaging evidence concerning their involvement in various tasks. Another possibility is to link our findings with more specific evidence concerning dorsal–ventral dissociations in the lateral PFC. As concerning the former, neuroimaging evidence has associated the dorsolateral sectors of PFC, including the BAs 8 and 9 with a variety of tasks, involving perceptual, attentional, imagistic, and mnemonic operations, but typically they have been associated with working memory tasks (see Cabeza and Nyberg, 2000, for a review). In addition, portions of BA 8 are thought to be part of the so-called frontal eye field, although the overlap between this region in human and nonhuman primates is still controversial (Koyoma et al., 2004). Interestingly, related to its role in emotional processing, BA 8 has been identified in tasks involving rating the pleasantness of facial stimuli (Nakamura et al., 1998). As concerning the role of ventrolateral PFC regions, including BA 47, their function has been associated with semantic memory operations, as well as with interference control and inhibitory processes (Miller and Cohen, 2001; Smith and Jonides, 1999; see also Cabeza and Nyberg, 2000). Specifically related to the involvement in emotional processing, right ventrolateral PFC has been implicated in the inhibition of negative emotions (Petrovic et al., 2002).

Turning to the evidence concerning the asymmetry in the dorsal–ventral dimension, two main views have been identified regarding the role of lateral PFC. According to one view, dorsolateral PFC regions are more involved in manipulating working memory contents whereas ventrolateral PFC regions are more involved in simple maintenance operations (D'Esposito et al., 2000; Owen et al., 1999; Petrides, 1995). Another view (Davidson and Irwin, 1999) specifically relates the function of lateral PFC to the role of emotion in guiding and organizing behavior in a motivationally consistent manner (Frijda, 1988). According to this view, dorsolateral PFC is involved in a particular form of working

memory—*affective working memory*—responsible for the representation of goal-related emotional states, whereas the ventrolateral sector of the PFC is involved in the simple representation of elementary emotional states (Davidson and Irwin, 1999).

Combining these ideas, one may speculate that the left dorso-lateral PFC activity for positive stimuli reflects the maintenance and manipulation of positive information in working memory during the valence-rating task, whereas the right ventrolateral PFC activity reflects the inhibition (avoidance) of negative information. Of course, these ideas are ad hoc and require independent confirmation. For instance, since other dorsolateral PFC regions were associated with evaluation of negative pictures, it would be important to clarify that working memory-related activity in the left PFC region specifically associated with positive pictures is related to the maintenance of appetitive goals (e.g., detection and processing of positive stimuli).

Dissociable regions of medial PFC were associated with arousal and positive valence

As illustrated by Fig. 2, dorsomedial PFC activity was sensitive to arousal, whereas ventromedial PFC activity was sensitive to positive valence. Previous evidence is consistent with the idea of possible segregation among medial PFC regions with respect to their involvement in emotional processing, but it is unclear whether the role of these regions is related to arousal or to valence. On the one hand, a metaanalysis of neuroimaging studies of emotion suggests that medial PFC regions are systematically activated by emotional stimuli, regardless of their valence (for a review, see Phan et al., 2002). This finding suggests a nonspecific involvement of medial PFC in emotional processing, probably mediated by arousal, and is consistent with some neuroimaging studies reporting dorsomedial activations associated with the processing of emotional stimuli, regardless of their valence (Lane et al., 1997a,b,c; Reiman, 1997; Reiman et al., 1997; Teasdale et al., 1999). On the other hand, another metaanalysis (Wager et al., 2003) found that, overall, medial PFC activity was associated with approach or appetitive tasks. Although approach-withdrawal and valence dimensions are not identical, they do overlap, and thus this finding suggests possible valence-related specificity in medial PFC function (see also George et al., 1995; Paradiso et al., 1999b). However, comparisons across studies are complicated by differences in stimuli, methods, and participants.

In the present study, we demonstrated a dorsal–ventral dissociation in the medial PFC, within-subjects and under controlled conditions. By identifying specific medial PFC regions sensitive to arousal and valence, this finding complements and reconciles previous functional neuroimaging evidence suggesting nonspecific (Lane et al., 1997a,b,c; Reiman, 1997; Reiman et al., 1997; Teasdale et al., 1999) versus valence-specific involvement of medial PFC during emotional processing (George et al., 1995; Paradiso et al., 1999b). This finding is also consistent with the results of an ERP study (Dolcos and Cabeza, 2002) where we found arousal versus valence dissociations at midline frontal electrodes. Although spatial resolution of ERP did not allow us to separate these effects topographically, it allowed dissociations in timing: there was a faster effect (500–800 ms) of positive valence (positive > negative = neutral) and a delayed effect (after 800 ms) of arousal (positive = negative > neutral). Since the valence-related ERP effect occurred in an earlier time-window (see also Cuthbert et al., 2000; Dillon et al., submitted), we interpreted it as reflecting

a bias toward detecting and processing positive stimuli. Given the fact that, overall, the medial PFC in the present study was more activated for positive than for negative pictures, this interpretation may also apply to the current finding.

An alternative account is that the sensitivity of medial PFC to positive valence reflected greater self-engagement in the processing of positive pictures compared to negative and neutral pictures. A number of recent neuroimaging studies associated medial PFC activity with self-referential processing (e.g., Cabeza et al., in press; Frith and Frith, 1999; Gusnard et al., 2001; Kelley et al., 2002). For instance, in a review of the literature, Frith and Frith (1999) suggested that activity in ventral medial PFC was specifically associated with emotional aspects of self-processing. It should be noted, however, that the appetitive and self-engagement accounts of the present medial PFC activation are compatible. For example, participants could have been more likely to relate the pictures to their own self and life in the case of positive pictures than in the case of negative and neutral pictures. The medial PFC region is frequently activated in functional neuroimaging studies of autobiographical memories. For example, we found this region to be more activated during the recognition of photographs taken by oneself than during the recognition of photographs taken by others (Cabeza et al., in press).

Arousal enhanced successful encoding activity in left PFC

Emotional arousal enhanced successful encoding (Dm) activity in lateral PFC. As illustrated by Fig. 3, compared to the Dm for neutral pictures, the Dm for arousing pictures was greater in left ventrolateral and dorsolateral PFC. These findings suggest that the enhancing effect of emotion on memory formation (i) is partly mediated by changes in PFC activity, (ii) is mainly related to arousal, and (iii) may involve an amplification of semantic processing and working memory operations mediated by lateral PFC regions.

Research on the neural bases of the enhancing effect of emotion on memory formation has emphasized the role of the amygdala and its interactions with MTL memory regions (Cahill et al., 1996; Canli et al., 2000, 2002; Dolcos et al., 2003, 2004; Hamann et al., 1999; Kilpatrick and Cahill, 2003; McGaugh et al., 2002). The present results expand this line of research by showing that the enhancing effect of emotion on memory formation is also mediated by changes in PFC activity. However, the effects of emotion on MTL and PFC are likely to enhance different memory mechanisms. Given the functions typically attributed to these regions (Moscovitch, 1992; Simons and Spiers, 2003), it is reasonable to assume that in MTL, emotion enhances the storage and consolidation of memory representations, whereas in PFC, it enhances strategic encoding processes.

A second implication of the present findings is that the enhancing effect of emotion on memory formation is primarily related to arousal rather than to valence. In our MTL study (Dolcos et al., 2003, 2004), we also found that the Dm increase was related to arousal rather than to valence. Thus, although valence-related Dm increases also occur, it seems fair to conclude that arousal is the main factor modulating the neural mechanisms of memory formation. This conclusion is consistent with our behavioral results, which showed that compared to non-arousing neutral pictures, memory is better for arousing positive and arousing negative pictures, with no significant difference between these two conditions. Thus, from the point of view of memory, a negative event can be as effective as a positive event (see also Talarico et al., in press).

The specific PFC regions where the Dm was increased by arousal suggest that arousing events are better remembered because they receive deeper semantic processing and working memory resources during encoding. The Dm was enhanced by arousal in left ventrolateral (BA 47) and dorsolateral (BA 9/6) PFC regions (see Fig. 3). The left ventrolateral region is an area that many functional neuroimaging studies have associated with encoding processes (for a review, see Cabeza and Nyberg, 2000), including event-related fMRI studies using the subsequent memory paradigm (Brewer et al., 1998; Kirchoff et al., 2000; Paller and Wagner, 2002; Wagner et al., 1998). Since the role of this region in encoding is generally attributed to semantic processing (Kapur et al., 1996; Poldrack et al., 1999; Shallice et al., 1994), the present finding suggests that arousal facilitated successful encoding by increasing semantic processing of the information in the pictures. It is possible that arousal also enhanced perceptual encoding processes mediated by right PFC (Brewer et al., 1998). However, since picture memory was tested using verbal recall, the effects of arousal on perceptual encoding were probably not detected. To detect such effects, it would be necessary to test memory with a nonverbal task, such as picture recognition (e.g., Brewer et al., 1998).

Finally, the effect of arousal on left dorsolateral PFC is likely to reflect the augmentation of the working memory processes typically associated with this region (D'Esposito et al., 2000; Owen et al., 1999; Petrides, 1995). Thus, it is possible that the contents of arousing events not only receive deeper semantic processing but are also maintained longer or manipulated more intensely in working memory, leading to better retention. It should be noted that this interpretation is compatible with the idea of dorsolateral PFC involvement during emotional evaluation of positive pictures, since the specific regions involved during positive evaluation versus successful encoding of arousing pictures are slightly different. It is possible that in one case, the involvement of working memory operations is related to the maintenance of appetitive-goals, whereas in the latter, the maintenance or manipulation of emotionally arousing information leads to better subsequent memory.

Conclusions

Using an fMRI paradigm that distinguished between activity related to emotional evaluation and emotional memory and between the effects of arousal and valence, the present study yielded three main results. First, during emotional evaluation, PFC activity showed a hemispheric asymmetry consistent with the valence hypothesis. A left dorsolateral PFC region was sensitive to positive valence, possibly reflecting the maintenance of positive information in working memory, whereas a right ventrolateral PFC region was sensitive to negative valence, possibly reflecting the inhibition of negative information. Second, dorsomedial PFC activity was sensitive to arousal, whereas ventromedial PFC activity was sensitive to positive valence, possibly reflecting the involvement of these regions in general processing of emotional information (dorsomedial PFC), and self-awareness or appetitive behavior (ventromedial PFC). Finally, successful encoding activity was enhanced by arousal in left ventrolateral and dorsolateral PFC regions, possibly reflecting an enhancement of strategic, semantic, and working memory operations. Although further research is required, these findings strongly suggest that different PFC regions are sensitive to arousal

and to valence, and that they play an important role in the evaluation of emotional stimuli and in processes that lead to better memory for emotional events.

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