Modulation of Memory Formation by Stimulus Content: Specific Role of the Medial Prefrontal Cortex in the Successful Encoding of Social Pictures

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Abstract

■ It is unclear whether the involvement of the medial prefrontal cortex (mPFC) during encoding is restricted to the evaluative processing of to-be-encoded stimuli or if it is instead actively engaged during memory formation. The difficulty of assessing the contribution of the mPFC to encoding based on previous neuroimaging studies partly arises from the use of several types of stimuli, such as emotional or social ones. These different types of stimulus content could differently modulate mPFC activity during memory formation and thus partly explain the variable contribution of this region to encoding. Using emotional/neutral and social/nonsocial pictures, we conducted an event-related functional magnetic resonance imaging study using a subsequent memory paradigm as the main analytical strategy. We observed that the brain activity in the dorsal and orbital mPFC is significantly and specifically predictive of the successful encoding of social compared with nonsocial pictures. In contrast, the activity in the amygdala specifically predicts the successful encoding of emotional compared with neutral pictures. The modulation of the mPFC by social information in a memory encoding context could be associated with the initiation of self-referential processes whose contribution is to enhance memory formation. ■

INTRODUCTION

The contribution of the prefrontal cortex (PFC) to episodic memory encoding has been studied extensively in the last decade and the primary focus of much of this work has been directed toward the PFC's dorsolateral and ventrolateral regions (Achim & Lepage, 2005; Habib, Nyberg, & Tulving, 2003; Fletcher & Henson, 2001; Yancey & Phelps, 2001; Buckner, Kelley, & Petersen, 1999; Kelley et al., 1998; Wagner, Poldrack, et al., 1998; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Interestingly, the medial PFC (mPFC) has recently received increasing attention in light of several findings implicating this region in memory formation. For instance, some researchers have suggested that the mPFC plays a direct role in emotional associative learning (Laviolette, Lipski, & Grace, 2005), self-referential encoding (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), and socially oriented encoding (Mitchell, Macrae, & Banaji, 2004). However, other investigators have not found any significant mPFC activation during encoding (Erk, Martin, & Walter, 2005) or have proposed that this region relates more to the capacity to evaluate future encoding success instead of being directly involved in memory formation (Kao, Davis, & Gabrieli, 2005).

Hence, it is unclear whether the involvement of the mPFC during encoding is restricted to an evaluative processing of to-be-encoded stimuli or if it is instead actively engaged in memory formation.

The difficulty of assessing the mPFC's contribution to memory encoding based on previous neuroimaging studies arises from the use of several types of stimuli, ranging from faces (Sergerie, Lepage, & Armony, 2005), to objects (Achim & Lepage, 2005), or to complex scenes (Dolcos, LaBar, & Cabeza, 2004a). Two types of stimulus content in particular have been associated with significant mPFC activation during picture viewing: emotional stimuli (Phan, Wager, Taylor, & Liberzon, 2002) and social stimuli (Adolphs, 1999). These two types of stimulus content could differently modulate the mPFC during memory formation and thus partly explain the variable contribution of this region to encoding, as observed in past studies. In the present study, we tested the specific effect of these two types of stimulus content on brain activity during encoding. The innovative aspect of our protocol was to manipulate the social content within the to-be-encoded stimuli while maintaining the emotional content constant across stimuli and vice versa. Based on recent studies (Norris, Chen, Zhu, Small, & Cacioppo, 2004; Geday, Gjedde, Boldsen, & Kupers, 2003), we defined social pictures as those showing at least one human being, whereas the nonsocial ones were characterized by the absence of any human

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being. Emotional pictures consisted of a set of stimuli that were previously rated in the positive or the negative valence category in a pilot study not described in this article. The majority of our pictures with social content show more than one human being and involve social interactions between two or more persons. Using these emotional/neutral and social/nonsocial pictures, we conducted an event-related functional magnetic resonance imaging (fMRI) study using a subsequent memory paradigm as the main analytical strategy (Paller & Wagner, 2002). This approach is the best method for distinguishing brain regions involved in memory formation (i.e., social pictures–hits vs. social pictures–misses) from those involved in stimulus perception/processing (i.e., social pictures vs. nonsocial pictures). Based on previous studies (Sergerie et al., 2005; Dolcos, LaBar, & Cabeza, 2004b; Mitchell et al., 2004), we hypothesized that the mPFC would be specifically involved in the successful encoding of social compared with nonsocial pictures. We predicted that the encoding of emotional compared with neutral pictures would be associated instead with significant activation of the amygdala.

METHODS

Subjects

Seventeen right-handed healthy volunteers (eight women and nine men; mean age = 25 years; years of education = 17) were recruited for this study. Subjects reported no history of psychiatric or neurological disorders, no history of drugs or alcohol abuse, and were not taking any psychotropic medications at the time of testing. The study was approved by the Montreal Neurological Hospital and Institute Ethics Committee, and informed written consent was obtained from all participants.

Stimuli

Two hundred forty color pictures were used in the experiment. These pictures were classified into six categories (40 pictures in each category): social content with a positive valence (i.e., pleasant events involving one or several persons), social neutral (events involving one or several persons and without apparent emotion), social negative (mostly sad events involving one or several persons), nonsocial positive (mostly beautiful landscapes), nonsocial neutral (household objects such as a fork or an umbrella), and nonsocial negative (scenes of destruction, guns, threatening animals). Pictures were selected from various sources, such as the International Affective Picture System (IAPS) (Lang, Greenwald, Bradley, & Hamm, 1993), the Empathy Picture System (EPS) (Geday et al., 2003), and from a series of pictures selected from our own collection. We measured the mean luminance for each picture category using CorelDraw software (Corel Corp., Ottawa, Canada). The luminance is basically the density of luminous intensity or the amount of light emitted from a particular area. There was no significant difference between the six groups of pictures regarding luminance [$F(5,240)$ = 0.21, p = .96]. Social pictures were matched on social complexity [i.e., the mean number ($\pm SD$) of persons seen on the picture; social neutral = 2.5 ± 1.7, social negative = 2.4 ± 1.4, social positive = 3.1 ± 1.1; main effect of valence regarding social complexity, $F(2,120)$ = 2.12, p = .11]. Because all picture stimuli from the IAPS and EPS were previously matched for general color composition and we included approximately the same number of these pictures in each stimulus category, we assumed that general color composition was matched across our experimental conditions. To avoid the potential confounding effect of arousal over emotional valence during encoding processes or a potential arousal level difference between social and nonsocial pictures, we excluded pictures known to trigger high arousal (based on previous pictures rating from the IAPS), such as pictures presenting erotic scenes or mutilated bodies. Finally, a seventh category made of 40 control pictures was added. Twenty social and 20 nonsocial pictures were randomly selected, and a series of transformations was applied (blur, pixelization, horizontal, and vertical inversion) using Adobe Photoshop 7.0 (Adobe Systems, San Jose, CA). Thus, 40 unrecognizable control pictures were obtained, matched for luminance and general color composition. These control pictures were included in our paradigm to provide a general overview of the brain regions involved in the viewing of complex pictures relative to abstract pictures.

Experimental Design

The experiment was divided in two parts: (1) an encoding phase and (2) a recognition test. In the encoding phase, 140 pictures from pregenerated list I or II (counterbalanced across subjects) (20 from each category, including control pictures) were pseudorandomly presented to the subjects, one at a time. Each picture was presented for 3 sec, followed by a fixation cross-presented for 2 sec. For each picture presentation, subjects were required to identify the presence of a human being within the picture by clicking on predetermined ''yes'' or ''no'' buttons. To maximize the brain activation associated with the viewing of the pictures, subjects were not explicitly told to learn or encode the pictures. Subjects were told to press anything when a control picture appeared. One of two different sets of pictures counterbalanced across subjects was presented in the encoding phase. The encoding phase was followed by a recognition test. Two hundred eighty pictures were presented for the recognition test, including

140 previously seen or old pictures and 140 new ones. As for the encoding phase, each picture was presented for 3 sec, followed by a fixation cross presented for 2 sec. Subjects were asked to identify the ''old'' pictures from the new ones by clicking on predetermined ''old'' or ''new'' buttons. The recognition test was conducted over two sessions of 140 pictures (70 old pictures and 70 new ones). Because the main focus of the present article is memory formation, we only report the fMRI data concerning the encoding phase.

After the scanning session, participants performed an emotional picture-rating task on a laptop computer. To get a more precise and idiosyncratic rating from subjects, each picture was accompanied by a continuous line with the label ''very negative'' at the left end of the line and the label ''very positive'' at the right end of the line. Subjects were further told that the middle of the line was associated with neutrality. Using a mouse, subjects moved an arrow on this line and clicked the left button once the arrow was well positioned on the line according to the emotional valence of the picture. This procedure indicated their personal emotional valence rating for each stimulus presented. The continuous line was in fact an ordinal scale ranging from 1 (*very negative*) to 323 (*very positive*). Mean valence values ($\pm SD$) for each condition were the following: nonsocial neutral = 163 ± 3.6, nonsocial negative = 91 ± 23.3, nonsocial positive = 239 ± 32.3, social neutral = 170 ± 16.6, social negative = 68 ± 20.6, and social positive = 261 ± 28.9. Mean valence values for combined neutral (167 ± 18.7), negative (79 ± 29.3), and positive (249 ± 18.1) pictures differed significantly among themselves [main effect of valence, $F(2,240) = 1142.79$, $p < .001$; Bonferroni = negative < neutral < positive]. Moreover, the emotional valence was not significantly different between social (169 ± 83.1) and nonsocial pictures (166 ± 63) [main effect of content, $F(1,240) = 0.07$, $p = .787$].

Data Acquisition

fMRI data were acquired at the Montreal Neurological Institute on a 1.5-T Siemens (Berlin, Germany) Sonata whole-body system equipped with a standard head coil, using gradient EPI sequences. A vacuum cushion stabilized the subject's head. Stimuli were generated by an IBM PC laptop computer running E-PRIME (Psychology Software Tools, Pittsburgh, PA) and projected via a LCD projector and mirror system. A mouse connected to the computer recorded the subject's responses. Functional T2*-weighted images were acquired with blood oxygenation level-dependent (BOLD) contrast (three functional runs of 278 volumes, TR = 2550 msec, TE = 50 msec, flip angle = 90°, field of view = 256 mm, matrix = 64 × 64), covering the entire brain (30 interleaved slices parallel to the anterior-posterior commissural plane; in plane resolution = 4 × 4 mm; thickness = 4 mm). After the functional session, a high-resolution T1-weighted anatomical volume was acquired using a gradient-echo pulse sequence (22 msec, TE = 9.2 msec, flip angle = 30°, voxel size = 1 × 1 × 1 mm).

Data Analysis

fMRI data were analyzed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Image preprocessing was done according to a standard procedure (Ashburner & Friston, 1997). Briefly, images were time corrected to account for differences in sampling times for different slices, realigned to the first volume to correct for interscan movement, and spatially normalized (voxel size = 2 × 2 × 2 mm) to the standard space of Talairach and Tournoux using the Montreal Neurological Institute template (Collins, Neelin, Peters, & Evans, 1994). Finally, the images were smoothed with an isotropic 8-mm full width half-maximum Gaussian kernel. Low-frequency temporal drifts were removed by applying a high-pass filter. Data were analyzed using the general linear model, in which individual events were modeled by a synthetic hemodynamic response function. For the encoding part of this study, three main analyses were conducted. In the first analysis, four event types were defined, based on the pictures' social content (social and nonsocial) and emotional context (neutral and emotional), as well as a fifth event type representing the control pictures. This first analysis allowed us to compare the brain activity associated with the viewing of the pictures at the encoding phase, that is, to identify the regions associated with the evaluative processing of emotional/social pictures compared with their respective neutral/nonsocial control pictures. We then performed analyses for the subsequent memory effect (SME). The SME analyses were conducted using the subjects' performance rates obtained in each condition during the memory recognition test. Two distinct analyses were performed for the SME: The first one was based on the social content of the picture (four event types: nonsocial ''subsequently remembered or hits,'' nonsocial ''subsequently forgotten or misses,'' social ''hits,'' and social ''misses''), and the second one was based on the emotional context (four event types based on the emotional conditions [neutral and emotional] and on the performance during recognition memory [hits and misses]). The number of forgotten pictures during the recognition test was very low for some subjects. Thus, some subjects have provided only two or three events for some pooled conditions/event types. We set a minimum cutoff of 10 events per pooled condition (i.e., at least 10 pictures had to be forgotten for the pooled neutral condition, which included social and nonsocial neutral pictures). Subjects that did not have enough

subsequently forgotten trials during encoding were not analyzed. Five of 17 subjects were excluded from SME analyses once this cutoff was applied. Linear contrasts of subject-specific parameter estimates for conditions of interest were generated and taken to a second-level random effects model. The threshold was set at $p < .001$ (uncorrected) for the first analysis and at $p < .001$ (one sample t tests) and $p < .005$ (uncorrected) (paired t tests) for the SME analyses.

To test the specific role of the amygdala in the successful encoding of emotional compared with neutral pictures and the specific role of the mPFC in the successful encoding of social compared with nonsocial pictures, we conducted two paired t tests: (1) (emotional hits vs. emotional misses) minus (neutral hits vs. neutral misses); (2) (social hits vs. social misses) minus (nonsocial hits vs. nonsocial misses). Inclusive masks consisting only of regions significantly involved in the successful encoding of emotional pictures or social pictures were used in the paired t tests. These inclusive masks were obtained from the contrasts (one-sample t tests, $p < .005$ uncorrected) "emotional hits minus emotional misses" and "social hits minus social misses" and were drawn using MRIcro software. Thus, the paired t tests identified the regions that were significantly more active in the successful encoding of emotional/social pictures than during the successful encoding of neutral/nonsocial pictures.

Finally, the parameter estimates of the BOLD signal observed in the peak voxel of the target regions obtained from the paired t tests were calculated for eight conditions of interest: (1) social hits, (2) social misses, (3) nonsocial hits, (4) nonsocial misses, (5) emotion hits, (6) emotion misses, (7) neutral hits, and (8) neutral misses. Using parameter estimates of all 12 subjects for all eight conditions, we conducted two distinct repeated measures analyses of variance (ANOVAs) (two levels within-subjects factors: memory factor [hits and misses] and content factor [social and nonsocial or emotional and neutral]) for each target region (thus, six distinct repeated-measures ANOVAs overall). Because SPM paired t tests are strictly for calculating a significant difference between two paired groups of contrasts, these BOLD signal analyses were added to test the more general main effects of memory and content on the brain activation for each target region. Moreover, the peak voxel of each target region was selected from a specific comparison, either ([social hits vs. social misses] vs. [nonsocial hits vs. nonsocial misses]) or ([emotional hits vs. emotional misses] vs. [neutral hits vs. neutral misses]). It was then important to test the BOLD signal for the "other comparison" and thus to clarify whether the absence of a significant difference in the target region for this latter comparison is explained by (1) an absence of modulation by encoding for both content conditions or (2) a general involvement in encoding for both content conditions.

RESULTS

Behavioral Performance

Performance during the encoding task (to determine the presence of a human being in the picture) was almost perfect for each subject at each condition. Only the nonsocial neutral pictures were not perfectly classified, with 99% accuracy. Moreover, no significant difference was observed in reaction time between content conditions (social vs. nonsocial) [$F(1,16) = 2.86$, $p = .11$] or among emotional conditions (positive, negative, and neutral) [$F(2,15) = 3.19$, $p = .07$]. There was no significant interaction between content and emotion regarding reaction time [$F(2,15) = 1.83$, $p = .17$]. During the recognition phase, the hit rate (used for SME analyses) did not significantly differ either between content conditions [$F(1,16) = 0.43$, $p = .52$] or between emotional conditions [$F(2,15) = 0.90$, $p = .43$] (nonsocial neutral, 86% of remembered pictures; nonsocial negative, 88%; nonsocial positive, 84%; social neutral, 85%; social negative, 85%; social positive, 85%). There was no significant interaction between content and emotion regarding the hit rate at the recognition phase [$F(2,15) = 1.71$, $p = .22$]. The mean percentage of hits (all conditions pooled together) obtained at the recognition phase by the 12 subjects included in the SME analyses was 82% (the worst individual performance mean was 72% of hits) compared with 92% for the five subjects excluded from the SME analyses.

Functional Magnetic Resonance Imaging Results

Picture Viewing

Before subsequent memory analyses, we first examined the brain activation specifically associated with the viewing (perceptive/evaluative processing) of social compared with nonsocial pictures and with the viewing of emotional (both positive and negative valence) compared with neutral pictures. The main regions showing activation associated with social picture viewing were located in the dorsal and ventral mPFC [Brodmann's areas (BA) 10/11, $t = 7.71$], the hippocampi ($t = 7.46$), the right fusiform gyrus (BA 37; $t = 6.90$), the posterior cingulate (BA 31; $t = 7.11$), the bilateral superior and middle temporal gyri (BA 37/38; $t = 10.59$), and the cuneus bilaterally (BA 18; $t = 9.17$). The reverse contrast (nonsocial vs. social) showed activations in the left middle frontal gyrus (BA 9; $t = 4.07$), the precuneus bilaterally (BA 7; $t = 8.65$), the bilateral inferior temporal gyri (BA 20; $t = 5.56$), the bilateral superior occipital gyri (BA 19; $t = 7.16$), and the cerebellum ($t = 9.15$). On the other hand, the emotional pictures specifically activated the mPFC (BA 9/10; $t = 5.03$), the left insula (BA 13; $t = 5.40$), the left amygdala ($t = 3.04$), the right ventrolateral PFC (BA 11; $t = 4.22$), the right fusiform gyrus (BA 37; $t = 9.05$), and the cuneus bilaterally (BA 18; $t = 7.57$) compared with the neutral pictures. The reverse

contrast (neutral vs. emotional) showed activations in the right inferior frontal gyrus (BA 11; $t = 4.59$), the right inferior temporal gyrus (BA 20; $t = 5.28$), the right inferior parietal lobule (BA 40; $t = 4.66$), and the left fusiform gyrus (BA 37; $t = 4.91$) (see Figure 1; all previous activations exceeded $p < .001$ on the single voxel level; 16 dF).

Subsequent Memory Effect

Using the contrast social hits versus social misses, we identified brain regions that were statistically predictive of the successful encoding of social pictures. These regions are the dorsomedial PFC bilaterally, the left ventrolateral PFC, the inferior frontal gyri bilaterally, the parahippocampal gyri, and the fusiform gyri bilaterally. The nonsocial hits versus nonsocial misses contrast was also performed and showed significant activations in the orbitofrontal and inferior (dorsolateral) frontal gyri bilaterally, the left hippocampus, the right parahippocampal gyrus, and the fusifom gyri bilaterally (see Table 1 for details).

Regions associated with the successful encoding of the emotional and neutral pictures were determined using the contrasts emotional hits versus emotional misses and neutral hits versus neutral misses. Successful encoding of the emotional pictures was associated with the activation of the superior and inferior frontal gyri, the amygdala bilaterally, the right parahippocampal gyrus, and the fusifom gyri bilaterally. The neutral pictures that were subsequently remembered during the recognition test were related to a greater activation of the left dorsal PFC, the right superior temporal gyrus, the left parahippocampal gyrus, and the fusiform gyri bilaterally compared with the subsequently forgotten neutral pictures (see Table 1 for details).

Paired t tests were conducted to identify brain regions specifically involved in the successful encoding of emotional compared with neutral pictures (contrast: [emotional hits vs. emotional misses] minus [neutral hits vs. neutral misses]) and social compared with nonsocial

pictures (contrast: [social hits vs. social misses] minus [nonsocial hits vs. nonsocial misses]). Two bilateral regions were significantly more involved in the successful encoding of emotional compared with neutral pictures: the amygdala ($t = 4.44$) and the fusiform gyri (BA 37; $t = 5.07$) (see Figure 2A). Three main regions appeared to be specific to the successful encoding of social pictures compared with the nonsocial ones: the right dorsomedial PFC (BA 10; $t = 3.37$), the orbital PFC and mPFC (BA 11; $t = 4.95$), and the left superior frontal gyrus (BA 8; $t = 5.70$) (see Figure 2B).

Parameter Estimates of the Blood Oxygenation Level-dependent Signal

The specificity of the amygdala for the successful encoding of emotional content and the specificity of the dorsal and orbital mPFC for the successful encoding of social content were also tested by calculating the parameter estimates of the BOLD activation observed in the peak voxel of each of these three regions (obtained from the paired t tests). For the dorsomedial PFC (peak voxel = 10, 56, 32), the repeated measures ANOVA comparing social and nonsocial conditions yielded a significant main effect of memory (hits vs. misses) [$F(1,11) = 6.20, p = .03$] and did not yield a significant main effect of content (social vs. nonsocial) [$F(1,11) = 0.15, p = .70$]. A significant Memory × Content interaction was also observed [$F(1,11) = 12.28, p = .005$], suggesting that a greater BOLD signal in the dorsomedial PFC was specific to the condition ''social hits'' (Figure 3A). Concerning the comparison between emotional and neutral conditions, a significant main effect was observed for the memory factor [$F(1,11) = 9.28, p = .01$], thus emphasizing the role of the dorsomedial PFC in encoding. However, no significant effect was observed either for the content factor [$F(1,11) = 1.45, p = .25$] or for the Memory × Content interaction [$F(1,11) = 0.33, p = .58$] (Figure 3B). This result suggests that the BOLD signal in the dorsomedial PFC was not significantly modulated by

Figure 1. Brain activation during the viewing of emotional pictures (left) compared to neutral ones (contrast: all emotional pictures vs. all neutral pictures) and during the viewing of social pictures (right) compared to nonsocial ones (contrast: all social pictures vs. all nonsocial pictures). Statistical parametric maps (one sample t test, 17 subjects analyzed) show significant activation at a statistical threshold of $p < .001$ (uncorrected) with 10 voxels as the minimal cluster size.
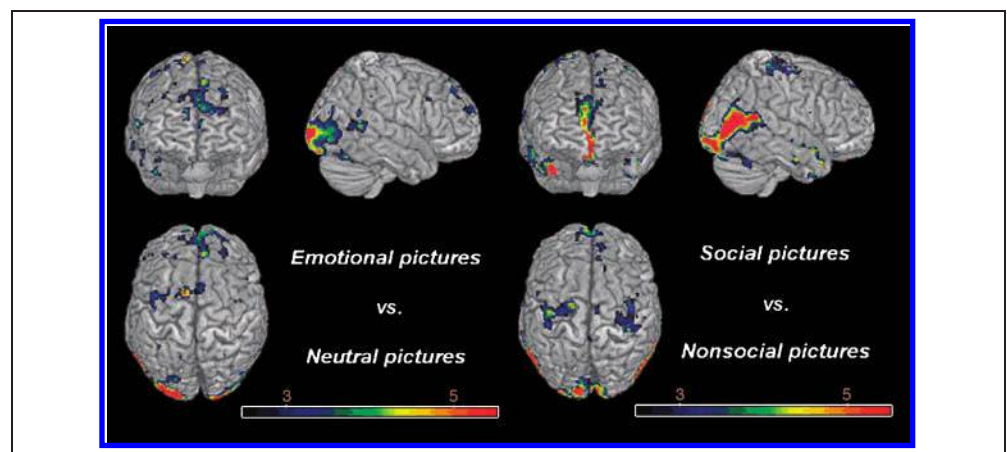

Emotional pictures vs. Neutral pictures

Social pictures vs. Nonsocial pictures

Table 1. Brain Activation Associated with the Successful Encoding (Subsequently Remembered [Hits] vs. Subsequently Forgotten [Misses]) of Social, Nonsocial, Emotional, and Neutral Pictures

| Brain Area | Hemisphere/BA | Stereotaxic Coordinates | | | t Value |
		x	*y*	*z*	
Social hits vs. social misses					
Dorsal PFC	L/10	−18	56	22	5.97
Dorsomedial PFC	R/9	10	60	34	3.84
Ventrolateral PFC	L/47	−44	38	−8	4.14
Inferior frontal gyri	L–R/45	60	18	18	4.58
Anterior parahippocampal gyrus	R/35	22	−6	−24	4.08
Posterior parahippocampal gyrus	L/28	−22	−18	−22	4.79
Fusiform gyri	L–R/37–19	−46	−72	−14	8.00
Nonsocial hits vs. nonsocial misses					
Middle frontal gyrus	L–R/11	26	34	−16	7.01
Dorsolateral PFC	L–R/9–44	46	12	30	3.61
Hippocampus	L	−24	−16	−12	3.79
Parahippocampal gyrus	R/36	32	−24	−26	4.90
Fusifom gyri	L–R/37	46	−62	−16	7.88
Emotional hits vs. emotional misses					
Superior frontal gyrus	L–R/11	−32	36	−12	5.32
Inferior frontal gyrus	L–R/8–9–46	−46	18	26	6.10
Amygdala	L–R	20	−4	−20	5.23
Parahippocampal gyrus	L–R/36	30	−26	−24	7.88
Fusiform gyri	L–R/37–19	−44	−52	−14	8.24
Neutral hits vs. neutral misses					
Dorsal PFC	L/10	−16	58	22	3.46
Superior temporal gyrus	R/22	58	6	4	4.57
Parahippocampal gyrus	L/28	−22	−6	−28	3.60
Fusiform gyri	L–R/37	48	−60	−16	6.49

Activations are reported if they exceeded $p < .001$ (uncorrected) on the single voxel level. Stereotaxic coordinates represent the peak height voxel of the cluster.

emotional content during encoding. Concerning the orbital PFC (peak voxel = −4, 38, −26), the repeated measures ANOVA comparing social and nonsocial conditions did not reveal a significant main effect of memory $[F(1,11) = 2.27, p = .16]$ or a significant main effect of content $[F(1,11) = 0.61, p = .45]$. It did, however, show a significant Memory × Content interaction $[F(1,11) = 22.88, p = .006]$ (Figure 3C). Again, this result points toward a specific involvement of the orbital PFC for the subsequently remembered social pictures. No significant

results were obtained from the comparison between emotional and neutral conditions in the orbital PFC [main effect of memory, $F(1,11) = 1.81, p = .21$; main effect of content, $F(1,11) = 0.02, p = .90$; Memory × Content interaction, $F(1,11) = 0.70, p = .42$] (Figure 3D). Like the dorsomedial PFC, the orbital PFC was not significantly modulated by the emotional content compared with neutral content during encoding.

BOLD activation analysis in the amygdala (peak voxel = 18, −6, −18) for the comparison between social and

Figure 2. (A) Main target region (amygdala; peak voxel = 18, −6, −18) specific to the successful encoding of emotional pictures compared to neutral ones (contrast: [emotional hits vs. emotional misses] minus [neutral hits vs. neutral misses]). (B) Target regions specific to the successful encoding of social pictures compared to nonsocial ones (dorsomedial PFC, peak voxel = 10, 56, 32; orbital PFC, peak voxel = −4, 38, −26) (contrast: [social hits vs. social misses] minus [nonsocial hits vs. nonsocial misses]). Statistical parametric maps (paired t tests, 12 subjects analyzed) show significant activation at a statistical threshold of $p < .005$ (uncorrected) with 10 voxels as the minimal cluster size.
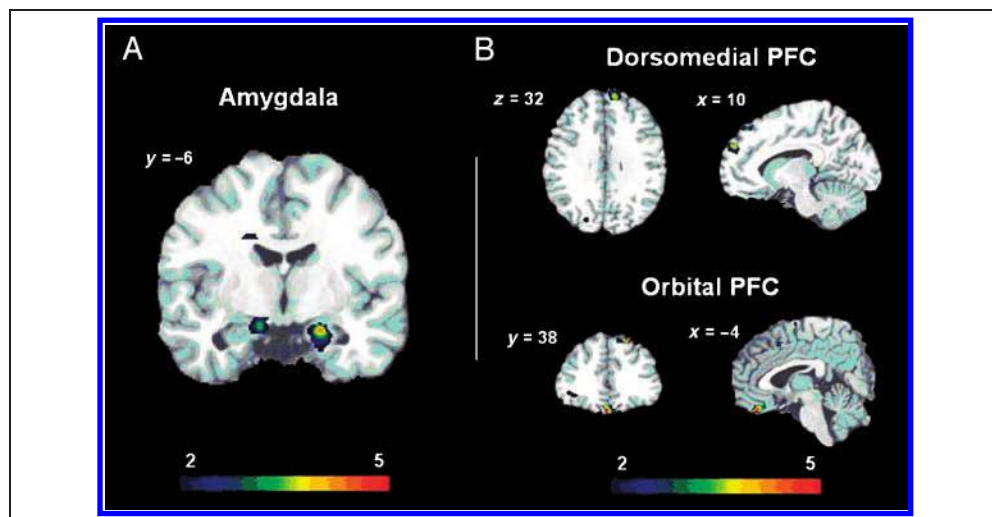

Figure 3. Parameter estimates of the BOLD signal observed in the peak voxel of the dorsomedial PFC (A and B), the orbital PFC (C and D), and the amygdala (E and F) for eight conditions of interest (social "hits," social "misses," nonsocial "hits," nonsocial "misses," emotion "hits," emotion "misses," neutral "hits," and neutral "misses"). Peak voxels were obtained from the contrast (social hits vs. social misses) minus (nonsocial hits vs. nonsocial misses) for the dorsomedial and the orbital PFC and from the contrast (emotional hits vs. emotional misses) minus (neutral hits vs. neutral misses) for the amygdala.
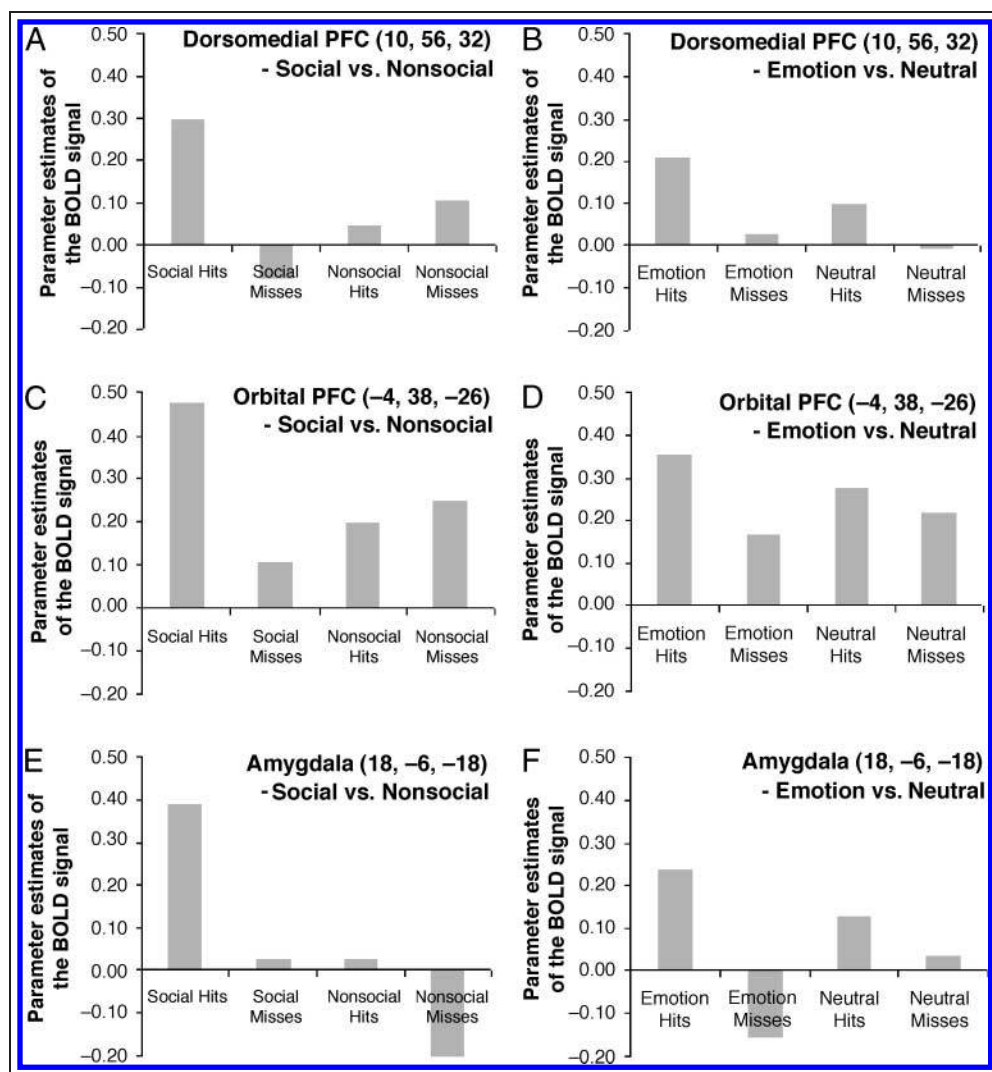
nonsocial conditions revealed significant main effects of memory [$F(1,11) = 10.14$, $p = .009$] and content [$F(1,11) = 13.13$, $p = .004$], but no significant Memory × Content interaction [$F(1,11) = 0.96$, $p = .34$] (Figure 3E). The significant main effect of memory shows that the amygdala was involved in the encoding of our pictures. Finally, the ANOVA comparing the emotional and the neutral conditions in the amygdala revealed a significant main effect of memory [$F(1,11) = 5.84$, $p = .034$], but no significant main effect of content [$F(1,11) = 0.14$, $p = .72$]. A significant Memory × Content interaction [$F(1,11) = 7.82$, $p = .017$] suggests a greater BOLD signal activation in the amygdala specifically for the emotional hits condition (Figure 3F).

In a post hoc analysis, we carried out a fixed-effect analysis with our 12 subjects. Eight independent conditions were defined: (1) socioemotional hits, (2) socioemotional misses, (3) socioneutral hits, (4) socioneutral misses, (5) nonsocial emotional hits, (6) nonsocial emotional misses, (7) nonsocial neutral hits, and (8) nonsocial neutral misses. Using SPM2 (SPM contrast manager), we calculated the triple interaction using the contrast "all-social hits versus all-social misses" as an inclusive mask (mask at 0.05 uncorrected). Thus, among the brain regions involved in the successful encoding of social pictures, we identified those showing a three-way Social Content × Emotional Content × Subsequent Memory interaction, that is, those significantly modulated by social content compared with emotional content during encoding. The only frontal regions showing such three-way interaction were in the superior frontal gyrus: lateral pole (−28, 64, 16; BA 10; $t = 2.30$) and dorsomedial part (8, 66, 24; BA 10; $t = 2.03$) ($p = .05$, uncorrected).

DISCUSSION

We observed that the brain activity in the mPFC is significantly and specifically predictive of the successful encoding of social compared with nonsocial pictures, but is not significantly implicated in the encoding of emotional compared with neutral pictures. Instead, the activity in the amygdala specifically predicts the successful encoding of emotional pictures.

Medial Prefrontal Cortex Contribution to the Successful Encoding of Social Stimuli

The mPFC is not only involved in the evaluative processing of social stimuli as suggested by the mPFC activation associated with the viewing of social pictures, but it is also actively engaged in the encoding of stimuli with social content. We suggest that social content, compared with nonsocial content, specifically modulates the contribution of the mPFC to episodic encoding.

The mPFC among other regions is a key structure involved in social processing (Gallagher & Frith, 2003;

Vogeley et al., 2001; Adolphs, 1999). Indeed, recent fMRI studies have demonstrated a major involvement of the mPFC in the judgment of socially relevant stimuli, from faces (Mitchell et al., 2004) to complex social interactions (Iacoboni et al., 2004). Some authors attribute this mPFC activation to the ability to evaluate the psychological state of other persons or oneself (Mitchell, Neil Macrae, & Banaji, 2005; Kelley et al., 2002). In a recent study supporting the involvement of the mPFC in social encoding, Mitchell et al. (2004) combined statements with faces for two different memory tasks: a socially oriented task (SOT) and a nonsocial task. Using SME analyses, they demonstrated the involvement of the dorsomedial PFC specifically during the SOT. Indeed, Mitchell et al. (2004) extracted the BOLD signal within the dorsomedial PFC and reported a significant 2 × 2 interaction (Memory Task × Subsequent Memory).

One methodological difference between the study of Mitchell et al. (2004) and the present one is the requirement for explicit complex social processing. Indeed, Mitchell et al.'s SOT-termed impression formation required participants to look at the faces and to use the statements to infer the personality traits of target persons. In another study, Mitchell et al. demonstrated that such SOT is specifically associated with dorsomedial PFC activation. One could argue that this type of socially oriented processing, although contributing to successful encoding when engaged, may not be absolutely necessary to successfully encode social stimuli. Our design used only one simple task in which social content was manipulated within the stimulus set. Thus, our subjects were not required to intentionally evaluate/process the psychological states depicted by the stimuli. In fact, the main conceptual difference between Mitchell et al. and the present study is about the factor that influences mPFC activity. Mitchell et al. manipulated the orienting task (impression formation vs. sequencing task) while the material was held constant. We instead kept the orienting task constant and made minimal demands on social processing while manipulating the presence or absence of people. Our study suggests that explicit complex socially relevant processing is not a necessary condition to observe a modulation of the dorsomedial PFC during memory formation. We found that the presence of people within a complex picture can modulate brain activity in this region. The fact that we found significant involvement of the dorsomedial PFC using a simple encoding task, as opposed to a SOT that triggers the judgment of mental characteristics, raises questions regarding potential implicit socially relevant processing that might be used to successfully encode social content.

The specific contribution of the orbital mPFC to the encoding of social pictures is also consistent with the literature. It has been demonstrated that patients with damage to the orbitofrontal cortex and the ventromedial PFC can have severe deficits in social functioning (Stone, Baron-Cohen, & Knight, 1998). These patients can still

express empathy, but they cannot connect their theory of mind inferences to an understanding of emotion. In other words, the orbitofrontal cortex is an essential brain structure for interpreting the valence and the significance of others actions and intentions (Rolls, 1996; Adolphs, Tranel, Damasio, & Damasio, 1994). Because 66% of our social pictures also have emotional content, it is possible that the interpretation of the emotional valence extracted from a social context favored the successful encoding of these social pictures and thus has prompted the orbital mPFC activation.

Self-referential Processing and Social Encoding

The involvement of the mPFC in social processing is complicated by the dual role of this region in both inferring the mental states of others (theory of mind) (Gallagher & Frith, 2003) and performing tasks that require people to introspect about their own inner mental states (self-referential) (Fossati et al., 2003; Kelley et al., 2002). A functional dissociation has been recently proposed by Schilbach et al., (2005), who have used dynamic virtual characters in fMRI to distinguish the neural correlates of being personally involved in social interaction (self-referential) as opposed to being a passive observer of social interaction between others (theory of mind) (Schilbach et al., 2005). Their results suggest that although the ventromedial PFC is associated with the analysis of social content as accessible in interactionally relevant gestures, differential activation of the dorsomedial PFC subserves the detection of self-reference. Based on these findings, the right dorsomedial PFC activation found in our study could suggest that implicit self-referential processes are part of the social encoding. Such a proposition is consistent with past studies that showed a reliable activation of the right dorsomedial PFC during self-referential encoding (Fossati et al., 2004; Macrae et al., 2004). In a meta-analysis of the self-referential effect, Symons and Johnson (1997) suggested that self-referential encoding has the potential to provide self-relevant category labels that may enhance subsequent recall by facilitating the reinstatement of encoding conditions at retrieval. Similarly, other researchers refer to this "self-relevant category labeling" as the simulation theory (Gallese & Goldman, 1998), which postulates that people use their own mental states to explain the mental processes of others. This implicit self-referential strategy to successfully encode pictures might be more automatic for social pictures compared with nonsocial ones and would likely modulate the involvement of the mPFC during social encoding.

Medial Prefrontal Cortex, Amygdala, and Emotional Encoding

The statistical comparison between the successful encoding of emotional stimuli versus neutral stimuli revealed a significant activation of the amygdala. The contribution of this structure to emotional encoding has been extensively documented in past studies (Dolcos et al., 2004a; Erk et al., 2003; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999). According to the modulation hypothesis, emotional encoding is linked to modulatory influences of the amygdala on encoding processes occurring in medial temporal lobe structures (McGaugh, McIntyre, & Power, 2002). Our paradigm did not show any significant activation of the mPFC during the encoding of emotional stimuli compared with neutral ones. Thus, our results could suggest that the mPFC is only involved in an evaluative processing of the emotional information (as suggested by the mPFC activation associated with the viewing of emotional pictures) and is not actively engaged in emotional encoding. A direct statistical comparison between social content and emotional content will be needed to confirm this hypothesis.

Based on our results, it appears that the amygdala plays a more general role in both emotional and social encoding. Indeed, even if the amygdala was not significantly involved in social encoding (paired t test), the post hoc parameter estimates analysis for the social versus nonsocial comparison does suggest a general involvement of the amygdala in the encoding of social pictures: (1) There is a significant main effect of memory, because the amygdala is more active for the subsequently remembered pictures compared with the forgotten ones. (2) There is also a significant main effect of content, because the amygdala is more active for the social pictures compared with nonsocial ones regardless of the encoding success. It is possible that social pictures are automatically processed as being potentially emotional. Indeed, social stimuli are likely the most emotionally evocative stimuli for humans and most brain regions subserving social processing are also implicated in emotional processing (Norris et al., 2004; Geday et al., 2003). Moreover, several studies suggest that the amygdala is implicated in the extraction of emotional meaning from social stimuli, in addition to general emotional processing (Winston, Strange, O'Doherty, & Dolan, 2002; Adolphs, Tranel, & Damasio, 1998). These observations underscore the highly dependent link between social and emotional processes.

Caveats and Limitations

One potential confound associated with the mPFC activation during social stimuli viewing is related to greater attentional demand. Because they are likely more complex, social stimuli may receive greater attention compared with nonsocial ones, and the dorsal mPFC activation could reflect this increase in attention (Bush, Luu, & Posner, 2000). Using an SME paradigm, we have directly compared social pictures with other social pictures. Reaction times and response accuracy during the encoding task were not statistically different

between subsequently remembered and forgotten pictures. Thus, we can safely assume that the attention level at the encoding phase was similar among pictures.

Another potential confound relates to the emotional valence of the subsequently remembered social pictures compared with the subsequently forgotten ones. Indeed, the mPFC activation could reflect a greater ratio of socioemotional pictures in the subsequently remembered subgroup. This is not the case because both subsequently remembered and subsequently forgotten social pictures had a proportion of 66% of socioemotional pictures. Similarly, one could argue that the social emotional pictures were perceived as being more emotional compared with the nonsocial emotional pictures. There was indeed a significant difference with respect to the emotional rating score between the social negative and the nonsocial negative pictures [68 vs. 91; $t(16) = 5.77$, $p < .01$]. However, there was no significant difference between the social positive and the nonsocial positive pictures [261 vs. 239; $t(16) = 1.19$, $p > .05$]. Moreover, a pilot study involving different subjects did not find such a difference in emotional rating between our social and nonsocial emotional pictures. Indeed, 12 healthy individuals used an ordinal scale ranging from 1 (*very negative*) to 7 (*very positive*) to rate the emotional valence of each picture presented on a computer monitor. Again, there was no significant difference between the social positive and the nonsocial positive pictures (5.66 vs. 5.83, $t = 0.85$, $df = 11$, $p > .05$) and no difference either between the social negative and the nonsocial negative pictures [1.96 vs. 2.08; $t(11) = 0.74$, $p > .05$]. Thus, although we cannot completely rule out the possibility that social emotional pictures were perceived as more emotional compared with nonsocial emotional pictures, we believe that it is unlikely that our results concerning the dorsomedial PFC were driven by such a small effect.

There is also a potential limitation associated with the orienting task used during the encoding phase. Subjects were explicitly requested to attend to the social aspects of the stimuli (''Is a human being present in the picture?'') but not to their emotional aspects. One can wonder if a potential difference regarding the level of processing (explicit vs. implicit) of these two types of content may partly explain the dorsomedial PFC modulation during the encoding of social content. Although this is possible, it is unlikely that the simple and quick identification of a human being in a picture will strongly promote complex social processing over and above emotional processing.

Finally, one problem with our recognition task was that some participants actually committed few mistakes. Even after the exclusion of five subjects who committed the fewest mistakes, we nonetheless had to pool some conditions for the SME analyses to respect a minimum cutoff of 10 events (mistakes) per condition. Pooling conditions led us to test the social factor and the emotional factor separately. As a result, the social and emotional content were not directly compared with each other but compared with their respective baseline (nonsocial and neutral). The SME result suggesting that the mPFC is a key region for social encoding cannot be interpreted as a statistical difference between social and emotional content, that is, a specific involvement of this region for social SME compared with emotional SME. To explore the potential specificity of the dorsomedial PFC for the encoding of social content compared with emotional content, we conducted a fixed-effect analysis that allowed us to define eight independent conditions: (1) socioemotional hits, (2) socioemotional misses, (3) socioneutral hits, (4) socioneutral misses, (5) nonsocial emotional hits, (6) nonsocial emotional misses, (7) nonsocial neutral hits, and (8) nonsocial neutral misses. We were then able to calculate the triple interaction (Social Content × Emotional Content × Subsequent Memory) among the regions involved in the successful encoding of social pictures. Although we used a very liberal threshold and we did not find a significant three-way interaction in the exact same dorsomedial PFC peak voxel as the one highlighted by the SME analysis (8, 66, 24, vs. 10, 56, 32), the results of this post hoc analysis suggest that the involvement of the dorsomedial PFC during memory formation may be specific to social content compared with emotional content. We anticipate that this result will be confirmed by future studies.

Conclusion

Specific areas of the brain support the process of memory formation depending on the characteristics of the to-be-encoded material (Macrae et al., 2004; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Kelley et al., 1998; Wagner, Schacter, et al., 1998). Although the modulatory effects of emotional information on memory performance and brain activity have been extensively studied (Smith, Henson, Dolan, & Rugg, 2004; Erk et al., 2003, 2005), only a limited amount of data concerning such modulatory influence of social information is available. Using an experimental design in which both social and emotional dimensions of stimulus content were systematically manipulated, we observed that the mPFC is modulated by social information and not significantly modulated by emotional information during successful memory encoding. This finding provides a heuristic explanation to the apparent heterogeneity of previous functional neuroimaging findings pertaining to mPFC involvement in memory encoding.

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