ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 21 (2004) 583–592

Orbitofrontal cortex tracks positive mood in mothers viewing pictures of their newborn infants

Jack B. Nitschke,[a,*] Eric E. Nelson,[b] Brett D. Rusch,[a] Andrew S. Fox,[a] Terrence R. Oakes,[a] and Richard J. Davidson[a]

[a] *W.M. Keck Laboratory for Functional Brain Imaging and Behavior and Laboratory for Affective Neuroscience, Departments of Psychiatry and Psychology, University of Wisconsin, Madison, WI 53705-2280, USA*
[b] *Section on Developmental Affective Neuroscience, Mood and Anxiety Disorders Program, National Institute of Mental Health, 20892-1381, USA*

Received 22 May 2003; revised 6 October 2003; accepted 6 October 2003

Positive affect elicited in a mother toward her newborn infant may be one of the most powerful and evolutionarily preserved forms of positive affect in the emotional landscape of human behavior. This study examined the neurobiology of this form of positive emotion and in so doing, sought to overcome the difficulty of eliciting robust positive affect in response to visual stimuli in the physiological laboratory. Six primiparous human mothers with no indications of postpartum depression brought their infants into the laboratory for a photo shoot. Approximately 6 weeks later, they viewed photographs of their infant, another infant, and adult faces during acquisition of functional magnetic resonance images (fMRI). Mothers exhibited bilateral activation of the orbitofrontal cortex (OFC) while viewing pictures of their own versus unfamiliar infants. While in the scanner, mothers rated their mood more positively for pictures of their own infants than for unfamiliar infants, adults, or at baseline. The orbitofrontal activation correlated positively with pleasant mood ratings. In contrast, areas of visual cortex that also discriminated between own and unfamiliar infants were unrelated to mood ratings. These data implicate the orbitofrontal cortex in a mother's affective responses to her infant, a form of positive emotion that has received scant attention in prior human neurobiological studies. Furthermore, individual variations in orbitofrontal activation to infant stimuli may reflect an important dimension of maternal attachment.

Keywords: Orbitofrontal cortex; Positive emotion; Infants; fMRI

Introduction

In contrast to the progress made investigating the neurobiology of various forms of negative emotion, tracking the circuitry governing positive emotion has been more elusive. Until very recently, knowledge about the neurobiology of positive emotion derived almost exclusively from research employing reward paradigms and pharmacological agents with nonhuman mammals (Gallagher et al., 1999; Ikemoto and Panksepp, 1999; Rolls, 1999a,b, 2000; Schoenbaum et al., 1998; Schultz, 1998; Schultz et al., 1997, 2000). With the increasing sophistication of neuroimaging paradigms, recent human studies have been highly consistent with nonhuman animal work in identifying the brain substrates associated with reward (Berns et al., 2001; Breiter et al., 2001; Bush et al., 2002; Delgado et al., 2000; Elliott et al., 2000, 2003; Gehring and Willoughby, 2002; Knutson et al., 2000, 2001a,b; McClure et al., 2003; O'Doherty et al., 2001a, 2002, 2003a; Pochon et al., 2002; Rogers et al., 1999; Thut et al., 1997; Zalla et al., 2000) and with drugs of abuse such as cocaine (Breiter et al., 1997; Childress et al., 1999; Garavan et al., 2000; Grant et al., 1996; Kilts et al., 2001; Wexler et al., 2001), procaine (Ketter et al., 1996; Servan-Schreiber et al., 1998), ecstasy (Gamma et al., 2000), and nicotine (Stein et al., 1998). Although important as an extension of the nonhuman animal research, these paradigms provide a limited sampling of positive emotion.

Other researchers have probed the neural circuitry of positive emotion via different paradigms. Two studies reported some overlapping brain activations in subjects asked to reexperience happy personal life events (Damasio et al., 2000; George et al., 1995). Other attempts to elicit positive emotion within the constraints of neuroimaging environments have measured responses to pleasant stimuli presented in various sensory modalities (Anderson et al., 2003; Bartels and Zeki, 2000; Garavan et al., 2001; Hamann and Mao, 2002; Hamann et al., 2002; Lane et al., 1997, 1999; O'Doherty et al., 2000, 2001b, 2002, 2003b; Paradiso et al., 1997, 1999; Schneider et al., 1997). As such, there has been progress in charting the neural bases of positive emotion in humans.

One form of positive emotion that has not been investigated in the relevant neuroimaging literature is the affect that arises in a mother's relationship with her infant. Whereas reward paradigms capitalize on approach tendencies and pursuit of an appetitive goal, the form of positive emotion in maternal attachment is better characterized by warmth, nurturance, joy, and fulfillment. This

* Corresponding author. W.M. Keck Laboratory for Functional Brain Imaging and Behavior, Waisman Center, Department of Psychiatry, University of Wisconsin, Room T-229, 1500 Highland Avenue, Madison, WI 53705-2280. Fax: +1-608-265-8737.
E-mail address: jnitschke@wisc.edu (J.B. Nitschke).
Available online on ScienceDirect (www.sciencedirect.com.)

1053-8119/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2003.10.005

form of positive affect is best described as post-goal attainment positive affect (Davidson et al., 2003). With the notable exception of women suffering from postpartum depression, most mothers report extremely strong pleasant emotions when interacting with or thinking about their infants. Accordingly, the intent of this study was to capture these high levels of attachment-related pleasant affect in mothers by showing them pictures of their smiling infant never before seen while concomitantly acquiring functional magnetic resonance imaging (fMRI) data. Since this form of positive affect is best described as post-goal attainment positive affect, we did not predict that its elicitation would be associated with lateralized dorsolateral prefrontal activation, a pattern previously observed during approach-related positive affect (Davidson et al., 2003). Rather, the orbitofrontal cortex (OFC) was of particular interest, based on prior research implicating that structure in various manifestations of positive emotion (Anderson et al., 2003; Breiter et al., 1997; Elliott et al., 2000, 2003; O'Doherty et al., 2000, 2001a,b, 2002, 2003a,b; Rolls, 1999a,b, 2000; Stein et al., 1998). In addition, mood ratings were obtained in the scanner while mothers viewed pictures of their infants to evaluate the hypothesis that individual differences in OFC activation would be associated with variations in pleasant affect elicited by the infant pictures.

Materials and methods

Subjects

Contact information for potentially eligible mothers was obtained from the Waisman Center Birth Registry at the University of Wisconsin. Letters describing the study and some of the eligibility criteria (e.g., primiparous, uncomplicated vaginal delivery, infant age of 2–4 months at time of letter) were mailed to over 50 mothers. Of the 14 who contacted us showing interest in participating in the study, 6 met additional eligibility criteria, including the absence of postpartum depression as determined by the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1996), being right-handed (Chapman and Chapman, 1987), no medical or neurological problems, no current medications, and no MRI contraindications (e.g., internal ferromagnetic devises, claustrophobia, back problems) and completed the fMRI session without complications. All mothers and adult acquaintances identified by them to participate in a photo shoot gave informed consent in accord with study approval by the Human Subjects Committee of the University of Wisconsin Medical School and were paid for their participation.

Experimental stimuli and paradigm

For the photograph stimuli, mothers came into the laboratory approximately 6 weeks before the fMRI session for a photo shoot with a digital camera, during which up to 150 pictures were taken of their 3- to 5-month-old infants while sitting in a baby seat. A similar photo shoot was conducted for an adult acquaintance (e.g., neighbor, work colleague), identified by each mother and having the same gender as that mother's infant. For each infant and acquaintance, 60 photographs with eye gaze on center were selected and individually cropped to minimize any differences in the physical characteristics of the picture stimuli across infants and adults (i.e., only entire head showing without clothing or jewelry) in preparation for presentation in the experimental paradigm of the fMRI session (see example stimuli in Fig. 1). The majority of infant stimuli were happy facial expressions. Adult acquaintance stimuli were either neutral or happy facial expressions.

At the fMRI session, mothers were shown picture stimuli of infants and adults while in the scanner. As shown in Fig. 1, an on–off block design was used alternating between pictures of a mother's own and an unfamiliar infant for two functional scans of the fMRI experiment. To control for familiarity, two additional functional scans alternated between pictures of an adult acquaintance identified by the mothers and an unfamiliar adult. Each functional scan was composed of 11 half-cycles, each lasting 30 s and containing five different photographs (6-s duration) of the same infant or adult. The photographs of each mother's infant and adult acquaintance served as control stimuli (i.e., unfamiliar infant, unfamiliar adult) for one other participant with an infant of the same gender, such that each mother of a pair saw identical stimuli. No picture was presented twice. The order of the four functional scans was the same for all mothers: infant, adult, infant, and adult.

While lying in the scanner, mothers rated their own mood on a nine-point scale (1 = not at all, 9 = extremely) for five descriptors—happy, warm, loving, motherly/nurturing, and excited—with a button box three times during each of the four functional scans: at the start of the scan, following the last 30-s half-cycle, and after a 30-s block of the alternate stimulus type not shown in the last half-cycle (Fig. 1). These ratings provided mood assessments at baseline and following each stimulus type. Functional images were not acquired during any of the mood ratings or during the final 30-s block of pictures. Upon conclusion of the functional scans, mothers made valence (0 = unpleasant, 3 = neutral, 6 = pleasant) and arousal ratings (0 = low, 3 = moderate, 6 = high) on a seven-point scale for 12 exemplars of each of the four stimulus types at a computer terminal outside the scanner.

fMRI acquisition

Anatomical and functional imaging was conducted on a General Electric EchoSpeed 1.5 T scanner (Milwaukee, WI) with a standard quadrature birdcage headcoil. For the whole-brain anatomical images, we used an axial T1-weighted three-dimensional spoiled gradient-recalled echo scan sequence [SPGR; TR/TE = 35/8 ms, flip angle (α) = 30°, number of excitations (NEX) = 1, field of view (FOV) = 24 × 24 cm, matrix = 256 × 192, slice thickness/gap = 1–1.2/0 mm, 124 slices]. For the whole-brain functional images, three coronal T2*-weighted echo-planar scan runs (EPI; TR/TE = 3000/50 ms, α = 90°, NEX = 1, FOV = 24 × 24 cm, matrix = 64 × 64, slice thickness/gap = 7/1 mm, in-plane resolution = 3.75 × 3.75 mm, 23 interleaved slices) were acquired using a gradient-echo pulse sequence for detecting blood oxygen level-dependent (BOLD) contrast. These acquisition parameters provided adequate signal recovery in certain areas vulnerable to the differential magnetic susceptibility coefficients of bone–air–tissue boundaries such as the lateral posterior OFC and amygdala but not in others (e.g., signal reduction was present in more medial or anterior regions of the OFC, ventromedial PFC, subgenual PFC, and the nucleus accumbens). All stimuli were presented through stereoscopic goggles using a Silent Vision

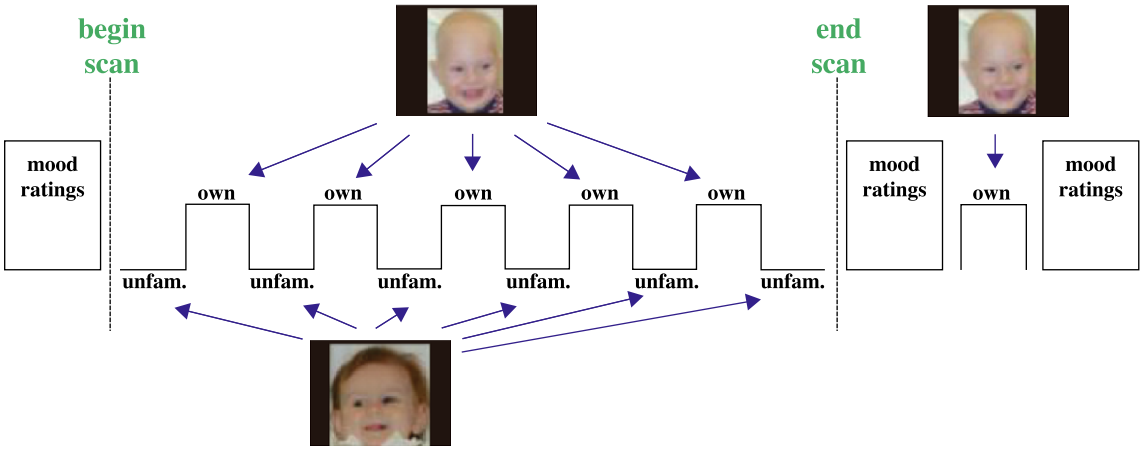

Fig. 1. Experimental design. Immediately before the start of each scan, each mother rated her mood on a nine-point scale (1 = not at all, 9 = extremely) for five descriptors—Happy, Warm, Loving, Motherly/Nurturing, and Excited—using a button box while lying in the scanner. fMRI data were then collected during the presentation of 30-s blocks of pictures alternating between each mother's own (top) and an unfamiliar (bottom) infant. Each 30-s block was comprised of five pictures shown for 6 s. The termination of the scan following the 11th block of pictures was followed by another set of mood ratings (after the unfamiliar infant in this case) and a final 30-s block of pictures and subsequent mood ratings (after mother's own infant in this case). Unfam. = unfamiliar.

system (Avotec, Inc., Jensen Beach, FL). A customized bite bar with dental impression compound affixed to an acrylic plate restricted head movement. Both the goggles and the bite bar were mounted directly to the headcoil. At a simulation session preceding the actual fMRI scanning session by approximately 1 week, mothers were fitted with the goggles and a bite bar before viewing an abbreviated version of the experimental paradigm while lying in a mock MRI scanner that included headcoil and digitized scanner sounds.

fMRI analysis

After off-line reconstruction, statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, UK) was employed to analyze the fMRI data. The time series for each voxel was interpolated to correct for nonsimultaneous slice acquisition within each volume. We corrected for three-dimensional motion using the first volume of a functional scan as the reference (Friston et al., 1995). The mean of all images for each

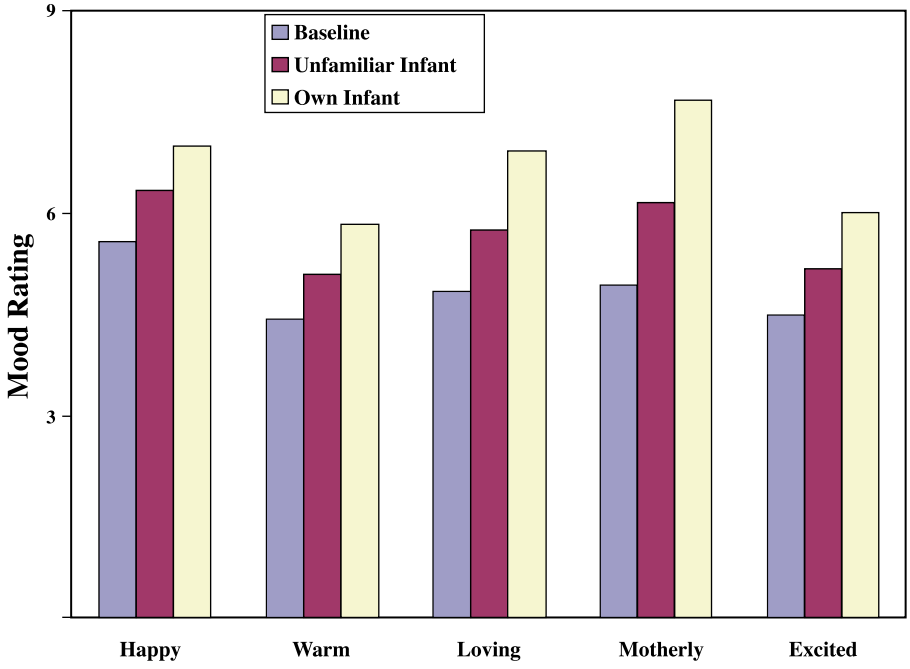

Fig. 2. Mood ratings indicating high levels of positive mood induced when mothers viewed their own infants. For all five descriptors assessed, mothers reported their moods to be more positive in response to their own infants than to unfamiliar infants, which in turn were more positive than for baseline ratings made before viewing pictures at the start of the scan. Higher values on the ordinate indicate more pleasant mood.

subject was normalized to a composite T2* template in Montreal Neurologic Institute (MNI) space and averaged to form a study-specific template (Friston et al., 1995). All data were spatially normalized to this template and resampled at a voxel size of 2 mm^3. Conversion into standardized Talairach space (Talairach and Tournoux, 1988) was implemented for Table 1. We then applied a nonisotropic three-dimensional Gaussian filter (full width at half maximum = 8, 8, 12).

For statistical analyses, the time series from each voxel were fitted to a boxcar reference function that was convolved with the standard hemodynamic response function provided by SPM99. The term "activation" refers to greater mean MR signal change during the viewing of one stimulus type (e.g., own infant) than the other stimulus type (e.g., unfamiliar infant) of the on–off block design for the fitted boxcar function. Temporal filtering was applied to the data using a high-pass filter with a width of twice the full cycle length and a low-pass filter using the frequency of a hemodynamic response function. Since the sample size was insufficient for conducting random-effect analyses, hypotheses were tested via fixed-effect analyses across all six subjects. These analyses yielded a statistical parametric map with voxel values corresponding to Student's t statistics for contrasts comparing photographs of own and unfamiliar infants and for contrasts comparing photographs of familiar and unfamiliar adults. Given the relatively small sample size, we employed stringent statistical criteria for thresholding the fMRI data in the group analyses, using $P < 0.001$ (corrected) and a minimum cluster size of 100 voxels (Forman et al., 1995). Because of their smaller size, subcortical structures were further inspected by relaxing the cluster thresholding criterion to 10 voxels. Those effects attaining significance for these criteria were subjected to additional analyses, including conjunction analyses, single-subject fixed-effects analyses, and correlations. Conjunction analyses based on the fixed-effect model were conducted at $P < 0.001$ (uncorrected) to test for activations that were consistently present across all subjects, to allow for population-based inferences (Friston et al., 1999). Correlational analyses tested for associations between MR signal change and mother's mood and picture ratings.

Results

Subjective ratings

Mothers' mood ratings while in the scanner were analyzed using a repeated-measures ANOVA with Picture Type (Infant, Adult), Scan (1, 2), Descriptor (Happy, Warm, Loving, Motherly/Nurturing, Excited), and Condition (Baseline, Familiar, Unfamiliar) as within-subjects factors. An ANOVA with Huynh–Feldt correction was used instead of the generally superior MANOVA strategy (Keselman, 1998; Vasey and Thayer, 1987) due to insufficient degrees of freedom for a MANOVA. Because there were four two-way interactions and one three-way interaction (as well as two additional interactions that were marginally significant), three-way ANOVAs were conducted for the infant and adult pictures separately with Scan (1, 2), Descriptor (Happy, Warm, Loving, Motherly/Nurturing, Excited), and Condition (Baseline, Familiar, Unfamiliar) as within-subjects factors. Pairwise comparisons were tested with paired Student's t tests. One-tailed distributions were uniformly used because directional effects were a priori predicted for mood ratings following own infant pictures compared to other conditions. Effect sizes were calculated for η^2 to assess the magnitude of the effects. As a variance-accounted-for effect size, η^2 is the proportion of the total variance that is attributed to an effect.

Ratings for the first infant scan were more pleasant than during the second infant scan [$F(1,5) = 12.14$, $P < 0.02$, $\eta^2 = 0.708$]. Collapsing across both infant scans, Fig. 2 illustrates the main effects for Descriptor [$F(4,20) = 11.02$, $P < 0.002$, $\eta^2 = 0.688$] and Condition [$F(2,10) = 19.04$, $P < 0.001$, $\eta^2 = 0.792$]. Baseline mood ratings were less pleasant than ratings after viewing one's own infant ($t = 7.50$, $P < 0.001$, $\eta^2 = 0.918$) and after viewing another infant ($t = 2.27$, $P < 0.04$, $\eta^2 = 0.507$). Mothers rated their mood to be more pleasant after viewing their own infant than after viewing an unfamiliar infant ($t = 3.86$, $P < 0.01$, $\eta^2 = 0.749$), a pattern observed for each of the descriptors (Happy, $t = 2.70$, $P < 0.03$; Warm, $t = 4.39$, $P < 0.004$; Loving, $t = 3.07$, $P < 0.02$; Motherly/Nurturing, $t = 3.67$, $P < 0.01$; Excited, $t = 2.99$, $P < 0.02$). A Scan × Condition interaction [$F(2,10) = 16.07$, $P < 0.002$] indicated elevated pleasant mood ratings for mothers' own infants across both scans ($t = 0.20$, $P > 0.40$), whereas baseline and unfamiliar infant ratings were more pleasant during the first than second infant scan ($t = 6.30$, $P < 0.001$, $\eta^2 = 0.888$, and $t = 2.59$, $P < 0.03$, $\eta^2 = 0.573$, respectively). The only other significant interaction was Scan × Descriptor, with greater variability in ratings among the descriptors for the first than third scan [$F(4,20) = 2.92$, $P < 0.05$].

The repeated-measures ANOVA for the adult pictures revealed a Condition effect with baseline ratings more pleasant than nearly identical ratings for the familiar and unfamiliar adults, which did not differ for any of the descriptors (ranging from $t = 0.00$ to 1.58, all P's > 0.17). The more pleasant baseline ratings likely reflect the residual mood effects of the preceding infant scans. A drop in baseline ratings before the fourth scan resulted in a Scan × Condition interaction [$F(2,10) = 4.26$, $P < 0.05$]. The only other effect was a Descriptor × Condition interaction with a particularly large discrepancy between baseline and adult ratings for motherly/nurturing [$F(8,40) = 5.75$, $P < 0.001$]. In addition, mood ratings following infant pictures were invariably much more pleasant than following adult pictures [ranging from $F(1,5) = 47.27–98.56$, all P's < 0.001, all $\eta^2 > 0.903$].

The picture ratings made outside of the scanner at the end of the experiment were analyzed for valence and arousal separately via Picture Type (Infant, Adult) × Condition (Familiar, Unfamiliar) repeated-measures ANOVAs. Both ANOVAs revealed almost identical patterns, with all main and interaction effects attaining significance, except for the Picture Type × Condition interaction in the ANOVA on arousal ratings, which was marginally significant at $P < 0.06$. Mothers rated pictures of their own infants (mean = 4.82, SD = 0.85) as being more pleasant than unfamiliar infants (mean = 3.38, SD = 0.35) ($t = 4.90$, $P < 0.003$, $\eta^2 = 0.828$). They also rated pictures of their own infants (mean = 4.28, SD = 1.33) as more arousing than unfamiliar infants (mean = 1.96, SD = 1.42) ($t = 2.86$, $P < 0.02$, $\eta^2 = 0.621$). Own infant pictures were rated more pleasant ($t = 4.66$, $P < 0.003$, $\eta^2 = 0.725$) and arousing ($t = 3.38$, $P < 0.01$, $\eta^2 = 0.705$) than familiar adult pictures (valence, mean = 3.07, SD = 0.21; arousal, mean = 1.55, SD = 1.39). No differences were observed between the two adult stimuli types or between unfamiliar infants and unfamiliar adults (ranging from $t = 0.78$ to 1.94, all P's > 0.11).

Neuroimaging results

Since the above analyses revealed that mothers reported more positive emotion in the first than second infant scan, fMRI data for each scan were analyzed separately. For the first infant scan, the contrast testing greater MR signal change to one's own than to an unfamiliar infant revealed bilateral OFC activation in the fixed-effects analysis across all subjects (Table 1). Fig. 3a illustrates that both the right and the left activations were in homologous sectors of the posterior lateral OFC and bordered the inferior frontal cortex. A conjunction analysis revealed smaller bilateral activations in the same posterior lateral OFC region ($P < 0.001$, uncorrected; Talairach coordinates for maximal values in left and right clusters are −32, 27, −10, and 32, 25, −10, respectively). For single-subject analyses contrasting own to unfamiliar infants, five of the six subjects showed activation of left ($P < 0.001$, uncorrected) and right OFC (four at $P < 0.001$ and one at $P < 0.05$, uncorrected); the remaining subject showed equivalent bilateral activation to both familiar and unfamiliar infants compared to a baseline blank screen at the start of each run. As would be expected, each of the six subjects showed greater OFC activation in response to their own infants compared with baseline (two at $P < 0.001$ and four at $P < 0.05$, uncorrected); however, only two of the six subjects showed greater OFC activation in response to unfamiliar infants compared with baseline ($P < 0.05$, uncorrected). Of further note, both OFC clusters were close to the boundary of signal dropout caused by proximity to tissue borders. Because the boundaries of detectable signal at the edges of the brain and near tissue borders are particularly sensitive to movement artifact, an additional fixed-effect analysis was conducted using regressors corresponding to the *x*, *y*, *z*, yaw, pitch, and roll dimensions to effectively remove variance due to movement. The same OFC regions on the left ($t = 5.29$, $P < 0.003$, corrected) and right ($t = 4.78$, $P < 0.02$, corrected) maintained significance. As shown in Figs. 3c–e, the second infant scan revealed a very similar pattern of OFC activation although not as pronounced, whereas the two adult scans did not.

Correlational analyses tested the hypothesis that OFC activation observed in the first infant scan would be associated with transient changes in pleasant mood elicited by the infant pictures. Several different methods for extracting MR values for the above OFC findings—peak voxel, average across each OFC cluster, average across spherical volume centered on and included within each OFC cluster—resulted in very similar correlations. The correlations below are reported for the average MR value across each OFC cluster. To assess the relative contributions of mood (i.e., emotion experience) and emotion perception to mothers' affective responses to the infant stimuli, we included measures of both processes. Valence and arousal ratings for the pictures were regressed out of the mood ratings made in the scanner, and these residualized mood ratings served as the measure of emotion experience. Conversely, the valence and arousal ratings with mood ratings residualized out served as the measure of emotion perception.

Fig. 4 illustrates positive associations between OFC activation and residualized pleasant mood ratings ($r = 0.68$, $P < 0.07$, and $r = 0.77$, $P < 0.04$, for the left and right OFC, respectively). For these correlations, mood ratings were averaged across the five mood descriptors before computing the difference between own and unfamiliar infant ratings analogous to the own versus unfamiliar contrast used for the fMRI analyses. No association was observed between either OFC cluster and the residualized valence or arousal ratings (r's between −0.38 and 0.36, all P's > 0.45). A correlational analysis conducted on a voxel-wise basis across the brain at $P < 0.01$ (uncorrected) revealed left and right OFC activations that were positively associated with pleasant mood ratings; however, no activated clusters in that analysis exceeded 85 voxels and the OFC clusters were less than 40 voxels.

The only other cluster implicated in the fixed-effects statistical parametric map for the own versus unfamiliar contrast in the first infant scan extended from occipital and temporal visual areas to the cerebellum (Fig. 3; Table 1). Conjunction and single-subject analyses at $P < 0.001$ (uncorrected) indicated that this cluster was consistently present across all six subjects. However, activation of this area was not correlated with residualized pleasant mood ratings ($r = 0.02$, $P > 0.48$). Instead, activation of this posterior cluster showed a marginally significant correlation with residualized arousal ratings ($r = 0.62$, $P < 0.10$). A very similar pattern was observed for a smaller visual cortex volume of interest (centered on the voxel of maximum activation) that did not include the cerebellum and was comparable in size (200 voxels) to the OFC clusters.

The second infant scan also revealed a posterior cluster including occipital, temporal, and cerebellar regions. It overlapped completely with the larger posterior cluster found for the first infant scan (Fig. 3). For the analogous conjunction analysis at $P < 0.001$ (uncorrected), smaller visual cortex and cerebellar activations were observed. Single-subject analyses revealed robust visual cortex activation at $P < 0.001$ (uncorrected) for three subjects,

Table 1
Brain regions showing activation during infant pictures

Brain region	Talairach coordinates			Cluster size in voxels	*t* value	*P* value (corrected)
	x	*y*	*z*			
Own infant–unfamiliar infant						
Bilateral OC[a] (BA 17/18/19)	8	−83	2	5,809	9.00	.000
Bilateral OC/TC[a] (BA 17/18/19/37)	36	−84	21	(5,809)	8.19	.000
Bilateral cerebellum[a]	6	−72	−8	(5,809)	8.10	.000
Left OFC (BA 11/47)	−40	32	−13	198	7.96	.000
Right OFC (BA 11/47)	34	31	−10	199	7.39	.000
Right OFC (BA 11/47)	44	32	−15	(199)	6.14	.000
Unfamiliar infant–own infant						
Right anterior TC (BA 20/21)	57	−33	−7	366	8.56	.000
Right anterior TC (BA 20/21)	61	−18	−11	(366)	7.23	.000
Left anterior TC (BA 20/21)	−57	−37	−2	325	7.84	.000

Note. Data shown are for the first infant scan using a statistical parametric map thresholded at $P < 0.001$ (corrected) and a minimum cluster size of 100 voxels (Forman et al., 1995). Talairach coordinates in millimeters (origin at anterior commissure): *x* = left(−) to right(+), *y* = posterior(−) to anterior(+), *z* = inferior(−) to superior(+). Cluster size in number of voxels. Voxel-level *t* values with corresponding corrected *P* values. OC = occipital cortex. TC = temporal cortex. OFC = orbitofrontal cortex. BA = Brodmann area.

[a] Regions included in posterior cluster.

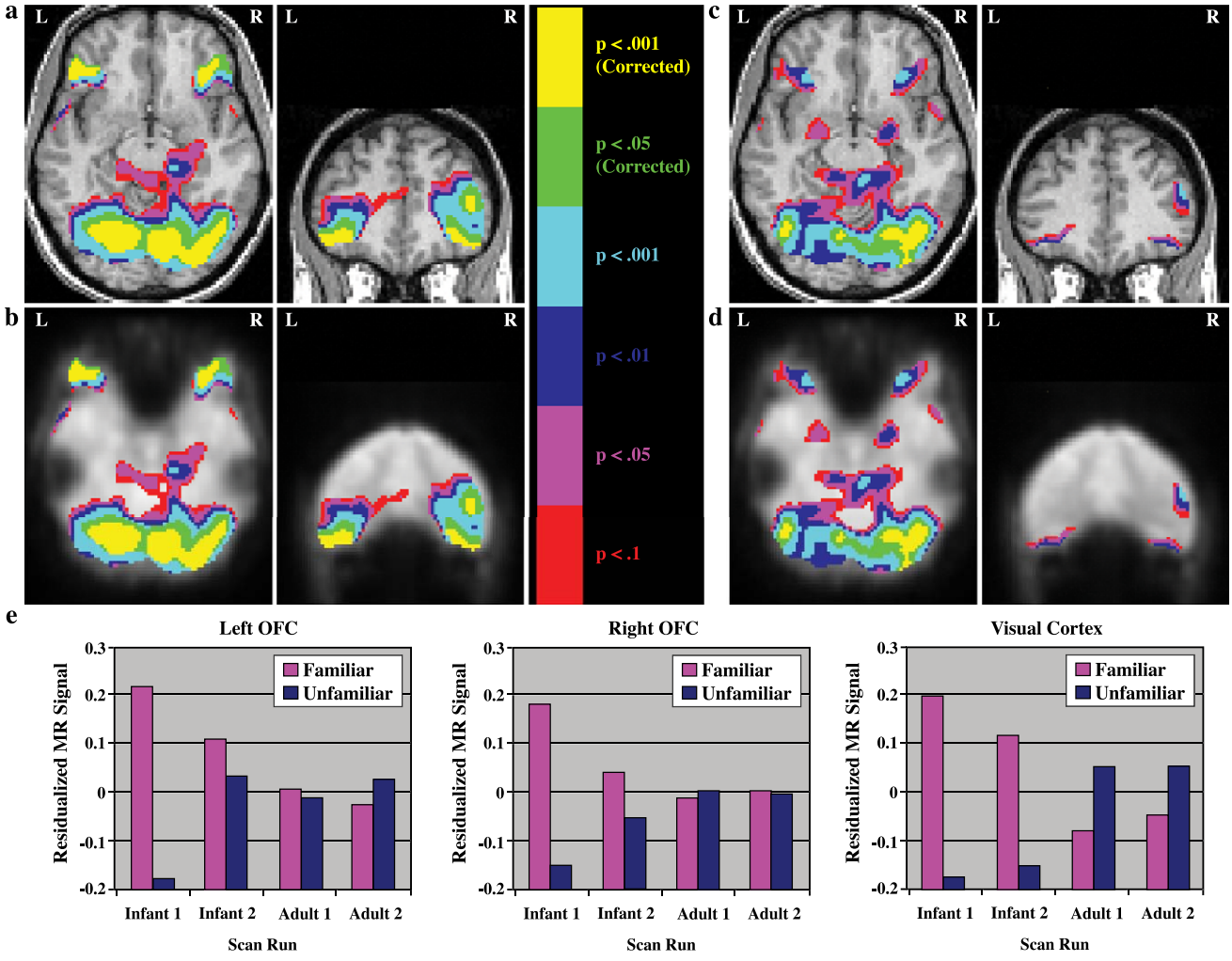

Fig. 3. Brain activation in mothers while viewing pictures of their own infants compared to unfamiliar infants. Bilateral activation in the orbitofrontal cortex during the first infant scan is depicted on anatomical images (a) and echo-planar images (b) in axial and coronal orientations. Similar orbitofrontal activations occurring during the second infant scan are shown on anatomical images (c) and echo-planar images (d) in axial and coronal orientations. All axial slices also show visual cortex activation. Effects of primary analysis are displayed in yellow, with effects at less stringent thresholds also shown for comparison (Jernigan et al., 2003). All images are displayed at intersection of voxel with maximal activation in the right orbitofrontal cortex for the first infant scan ($x = -40$, $y = 32$, $z = -13$, Talairach coordinates in millimeters with origin at anterior commissure: x = left[−] to right[+], y = posterior[−] to anterior[+], z = inferior[−] to superior[+]). (e) Plots for each of the clusters observed in the first infant scan ($P < 0.001$, corrected) depict MR signal for familiar and unfamiliar conditions in all infant and adult scans. OFC = Orbitofrontal cortex.

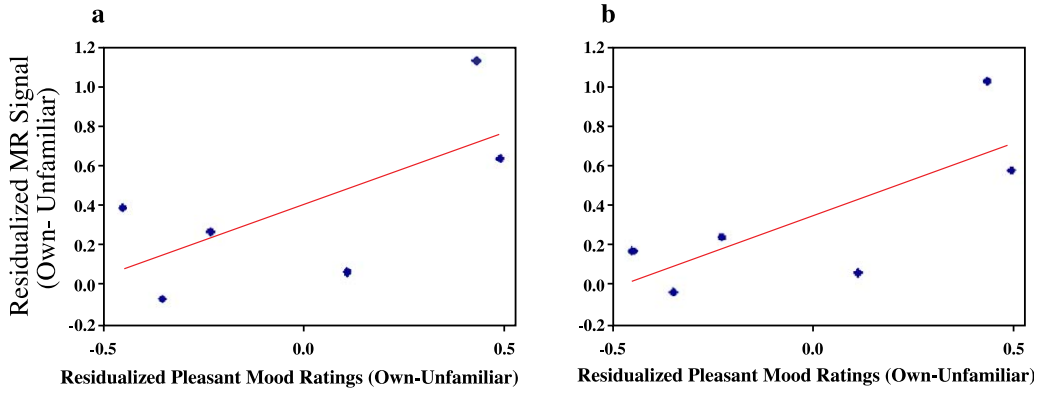

Fig. 4. Scatter plots showing the strong positive relationship between pleasant mood ratings and MR signal change in (a) left orbitofrontal cortex, $r = 0.68$, and (b) right orbitofrontal cortex, $r = 0.77$. Higher values on the ordinate indicate greater MR signal change to mothers' own than unfamiliar infants for the orbitofrontal clusters at $P < 0.001$ (corrected) depicted in Fig. 3a. Higher values on the abscissa indicate more pleasant mood to mothers' own than unfamiliar infants (with mothers' valence and arousal ratings of the infant pictures residualized out).

whereas the other three subjects only showed activation of the visual cortex accompanying widespread brain activation at $P < 0.05$ (uncorrected).

As shown for the first infant scan in Table 1, presentation of an unfamiliar infant activated bilateral inferior temporal regions more than one's own infant. The inferior temporal activations were anterior to the temporal activations observed in response to mothers' own infants. The same temporal activations were observed for a conjunction analysis. Single-subject analyses contrasting unfamiliar to own infants revealed that each mother showed bilateral inferior temporal activation (at $P < 0.001$ except for one subject with left activation at $P < 0.05$, uncorrected). Although no activations fully met thresholding criteria for the second infant scan, bilateral inferior temporal activations were observed at less stringent thresholding criteria. At $P < 0.001$ (corrected), the cluster size for the right and left inferior temporal activations was 46 and 13 voxels, respectively. At $P < 0.05$ (corrected), those clusters were 270 and 159 voxels, respectively.

Neither adult scan showed significant effects at $P < 0.001$ (corrected) or $P < 0.05$ (corrected). Relaxing the statistical threshold to $P < 0.001$ (uncorrected) for the first adult scan resulted in three clusters exceeding 100 voxels that showed more activation for familiar than unfamiliar adults. The left and right occipital and right temporal/cerebellar regions overlapped completely with those more activated for own than unfamiliar infants. No OFC or lateral PFC findings were observed even when the spatial threshold was reduced to 1 voxel. The same three regions also activated during the second adult scan at $P < 0.001$ (uncorrected), as did left temporal/cerebellar and bilateral posterior parietal regions. The opposite adult contrast testing activation to unfamiliar adults revealed no reliably activated clusters at $P < 0.001$ (uncorrected) for the first adult scan, whereas the second adult scan revealed dorsal anterior cingulate and left insula activations.

No subcortical activations exceeding 10 voxels were observed for the analyses conducted on the infant or adult scans at $P < 0.001$ (corrected) or at $P < 0.05$ (corrected). The bilateral dorsal amygdala activation to mothers' own infants for the second infant scan shown in Fig. 3c was not observed at more conservative statistical thresholds. Because some previous studies have reported associations between amygdala activation and positive affect (Baxter and Murray, 2002; Garavan et al., 2001; Hamann and Mao, 2002; Hamann et al., 2002; Petrovich and Gallagher, 2003; Zalla et al., 2000), additional analyses at $P < 0.05$ (uncorrected) were conducted on an exploratory basis. There was no evidence of amygdala activation during the first infant or first adult scan, and the left amygdala activated more for familiar than unfamiliar adults during the second adult scan. Given the inconclusive results at this liberal statistical threshold, no further discussion is provided for the involvement of the amygdala in this paradigm.

Discussion

In an attempt to reliably elicit a form of positive emotion related to maternal attachment, first-time mothers were shown photographs of their 3- to 5-month-old infants that they had never before seen. To interrogate the neural circuitry recruited during the positive emotion elicited in these mothers, fMRI was employed to contrast brain activity during the viewing of pictures of one's own infant and pictures of an unfamiliar infant of the same gender. Mothers' on-line ratings of pleasant mood while in the scanner provided direct evidence that the hedonic manipulation in the present study was successful. Viewing the pictures resulted in pronounced transient changes in mothers' moods, with significance tests and large effect sizes indicating more positive emotion reported after viewing pictures of their own infants than after viewing pictures of unfamiliar infants, adults, or baseline periods before picture display. Photographs of mothers' own infants resulted in reliable bilateral activation of the OFC. The strong positive association between this OFC activation and pleasant mood while viewing the infant pictures further implicates the OFC in maternal affective responses to their infants. In contrast, areas of visual cortex that also discriminated between own and unfamiliar infants were unrelated to mood ratings.

Recruitment of the bilateral OFC in all six mothers during the positive emotion elicited by viewing one's own infant is consistent with the proposed role of the OFC in decoding the affective value of a stimulus or event (Rolls, 1999a,b, 2000). This finding adds to the growing corpus of human data implicating the OFC in various forms of positive as well as negative emotion. Replicating the extensive work on reward processing in nonhuman mammals (Gallagher et al., 1999; Rolls, 1999a,b, 2000; Schoenbaum et al., 1998; Schultz et al., 2000), similar paradigms with humans have activated different sectors of the OFC using taste (Berns et al., 2001; McClure et al., 2003; O'Doherty et al., 2001b, 2002, 2003a; Small et al., 2001), smell (Anderson et al., 2003; O'Doherty et al., 2000), money (Breiter et al., 2001; Elliott et al., 2000, 2003; Knutson et al., 2001b; O'Doherty et al., 2001a; Thut et al., 1997), nonmonetary gambling (Rogers et al., 1999), and positive feedback on a detection task (Zalla et al., 2000). In a very different experimental manipulation of positive emotion, administration of cocaine to cocaine users (Breiter et al., 1997) and nicotine to smokers (Stein et al., 1998) has also been shown to activate the OFC. The posterior lateral locus of the current findings for positive affect in maternal attachment provides further corroborating evidence of the OFC as a key structure in the neural circuitry of positive emotion. Moreover, our data indicate that the magnitude of activation elicited in response to own versus unfamiliar infants in this sector of the OFC faithfully tracks the intensity of positive mood reported by mothers while viewing pictures of their infants compared with pictures of unfamiliar infants. This and other studies identifying distinct OFC regions associated with different forms of positive emotion (e.g., Anderson et al., 2003; Elliott et al., 2003; O'Doherty et al., 2001a) underscore the heterogeneity of positive affect and its neural substrates.

In light of our previous work on laterality in emotion (Davidson, 2000; Heller et al., 1998), the bilateral nature of the OFC activation in the present study points to the need for specificity in two regards. First, prior research on emotion has not reliably observed laterality effects for the OFC, with most reports instead implicating the dorsolateral prefrontal and anterior temporal regions. Second, relevant research has documented laterality effects for approach-related positive affect (Davidson et al., 1990; Harmon-Jones and Allen, 1997; Miller and Tomarken, 2001; Sutton and Davidson, 1997; Tomarken et al., 1992; Urry et al., in press). Approach tendencies are not central for the positive affect accompanying maternal attachment, which involves appreciation and enjoyment rather than pursuit of a desired objective, especially as operationalized in the current paradigm.

The mood rating and neuroimaging data from this experiment bear on temporal characteristics of positive emotion. The overall

reduction in mothers' ratings of their positive mood from the first to second infant scan indicates that positive emotion elicited by pleasant stimuli diminishes with repeated exposure to similar stimuli. However, emotional responses to their own infants remained elevated throughout the experiment, suggesting that attachment-related positive affect is less susceptible to habituation. Both infant scans revealed a highly similar pattern of OFC and visual cortex activation, though somewhat less pronounced in the second infant scan. Further research is needed to characterize the chronometry of different forms of positive affect and to interrogate how temporal variations are instantiated in the OFC and other brain regions involved in positive emotion.

In addition to the OFC regions, visual cortical areas activated more to mothers' own than unfamiliar infants. However, mothers' on-line mood ratings showed no relationship with activation in these visual areas. Instead, greater MR signal change was associated with emotion perception processes related to the photographs' perceived level of arousal, consistent with fMRI data for standardized emotional pictures (Lang et al., 1998). Differences in visual scanning patterns may also help account for the differential activation in visual cortices. Included in this activated cluster was the fusiform area as observed for the scan comparing familiar and unfamiliar adults, consistent with some previous reports (Henson et al., 2000) but not others (Leveroni et al., 2002; Rossion et al., 2001). The bilateral inferior temporal activation to unfamiliar infants is in the same cortical area reported for viewing unfamiliar adult faces (Rossion et al., 2001). Although familiarity may account for some of the posterior activation observed, it is not a likely contributor to the OFC findings based on the fMRI data for the adult scans depicted in Fig. 3e, the association found between OFC activation and pleasant mood when viewing pictures of familiar and unfamiliar infants, and extant knowledge about OFC function.

A potential alternative explanation for the visual cortex activation resulting from greater stimulus complexity in the photographs of one's own infant than the unfamiliar infant was ruled out by the experimental design employed. Each mother's own infant and familiar adult pictures served as the unfamiliar infant and adult pictures for one other participating mother such that each mother of a pair viewed identical stimuli. In addition, to further insure that brain activation patterns could not be explained by differences in the physical characteristics of the photographs used, extreme care was taken in selecting photographs with eye gaze on center and with pleasant facial expressions and in cropping photographs such that only the entire head was visible while any clothing or other objects were excluded.

Further research using recently developed pulse sequences to reduce signal dropout resulting from susceptibility artifact and scanning at higher field strength is needed to determine whether the bilateral OFC activation observed may extend into more medial and anterior sectors of the OFC and into the nucleus accumbens. Present data also point to the importance of careful measurement of nonphysiological emotional responses in neuroimaging research. Mood ratings were made in the scanner when the emotional stimuli were first presented, avoiding the pitfalls of obtaining retrospective reports of mood (Kahneman, 1999). In addition, we assessed both emotional experience and emotional perception processes and found them to be uniquely associated with activation of distinct brain regions.

Rolls (1999a) has implicated the OFC in the representation of primary rewards and punishments. Most of the extant data in nonhuman species have focused on nonsocial incentives. The present study extends this work by highlighting the role of the OFC in the representation of attachment-related positive affect (Bowlby, 1982). Moreover, the fact that the magnitude of OFC activation strongly predicts the intensity of positive mood reported by mothers in response to pictures of their own versus unfamiliar infants underscores two important issues. First, MR signal change in the OFC appears to linearly track the intensity of positive emotions that may underlie maternal attachment. Second, individual differences in MR signal change in the OFC in response to positive stimuli, particularly those selected in an idiographic manner, may be used to objectively assess individual differences in positive affective style (Davidson, 2000). Such individual differences may have important relevance for happiness and well-being as well as clinical implications, particularly in the assessment and prediction of postpartum depression.

Acknowledgments

We gratefully acknowledge Michael Anderle, Rebecca Beese, Krystal Cleven, Kelli Ferber, Wil Irwin, John Koger, Kristen Mackiewicz, Adrian Pederson, Alissa Possin, Hillary Schaefer, and Brian Skinner for their contributions to this project and Kristin Buss for comments on an earlier version of the manuscript. JBN was supported by an NIMH Career Development Award (K08-MH63984) and a Training Program in Emotion Research NIMH grant (T32-MH18931). This work was also supported by a grant from the Fetzer Institute to JBN and by NIMH grants (MH40747, P50-MH52354, MH43454) and an NIMH Research Scientist Award (K05-MH00875) to RJD. Parts of this work were presented at the annual meetings of Human Brain Mapping, Cambridge, England, June, 2001, of the Society for Personality and Social Psychology in Savannah, GA, February, 2002, and of the Society for Psychophysiological Research in Washington, DC, October, 2002.

References

Anderson, A.K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D.G., Glover, G., Gabrieli, J.D.E., Sobel, N., 2003. Dissociated neural representations of intensity and valence in human olfaction. Nat. Neurosci. 6, 196–202.

Bartels, A., Zeki, S., 2000. The neural basis of romantic love. NeuroReport 11, 3829–3834.

Baxter, M.G., Murray, E.A., 2002. The amygdala and reward. Nat. Rev., Neurosci. 7, 563–573.

Berns, G.S., McGlure, M., Pagnoni, G., Montague, P.R., 2001. Predictability modulates human brain responses to reward. J. Neurosci. 21, 2793–2798.

Bowlby, J., 1982. Attachment. Basic Books, New York.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. Neuron 19, 591–611.

Breiter, H.C., Aharon, I., Kahneman, D., Anders, D., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30, 619–639.

Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc. Natl. Acad. Sci. 99, 523–528.

Chapman, L.J., Chapman, J.P., 1987. The measurement of handedness. Brain Cogn. 6, 175–183.
Childress, A.R., Mozley, P.D., McElgin, W., Fitzgerald, J., Relvich, M., O'Brien, C.P., 1999. Limbic activation during cue-induced cocaine craving. Am. J. Psychiatry 156, 11–18.
Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L.B., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat. Neurosci. 3, 1049–1056.
Davidson, R.J., 2000. Affective style, psychopathology and resilience: brain mechanisms and plasticity. Am. Psychol. 55, 1196–1214.
Davidson, R.J., Ekman, P., Sarona, C., Senulis, J., Friesen, W.V., 1990. Approach/withdrawal and cerebral asymmetry: emotional expression and brain physiology, I. J. Pers. Soc. Psychol. 58, 330–341.
Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Kalin, N.H., 2003. Parsing the subcomponents of emotion and disorders of emotion: perspectives from affective neuroscience. In: Davidson, R.J., Scherer, K.R., Goldsmith, H.H. (Eds.), Handbook of Affective Sciences. Oxford Univ. Press, New York, pp. 8–24.
Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. J. Neurophysiol. 84, 3072–3077.
Elliott, R., Friston, K.J., Dolan, R.J., 2000. Dissociable neural responses in human reward systems. J. Neurosci. 20, 6159–6165.
Elliott, R., Newman, J.L., Longe, O.A., Deakin, J.F.W., 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. J. Neurosci. 23, 303–307.
First, M.G., Gibbon, M., Spitzer, R., Williams, J., 1996. User's Guide for the Structured Clinical Interview for the DSM-IV Axis I Disorders—Research Version. Biometrics Research Dept., New York.
Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn. Reson. Med. 33, 637–647.
Friston, K.J., Ashburner, J., Poline, J.B., Frith, C.D., Heather, J.D., Frackowiak, R.S., 1995. Spatial registration and normalisation of images. Hum. Brain Mapp. 2, 165–189.
Friston, K.J., Holmes, A.P., Worsley, K.J., 1999. How many subjects constitutes a study? NeuroImage 10, 1–5.
Gallagher, M., McMahan, R.W., Schoenbaum, G., 1999. Orbitofrontal cortex and representation of incentive values in associative learning. J. Neurosci. 19, 6610–6614.
Gamma, A., Frei, E., Lehmann, D., Pascual-Marqui, R.D., Hell, D., Vollenweider, F.X., 2000. Mood state and brain electric activity in ecstasy users. NeuroReport 11, 157–162.
Garavan, H., Pankiewicz, J., Bloom, A., Cho, J., Sperry, L., Ross, T.J., Salmeron, B.J., Risinger, R., Kelley, D., Stein, E.A., 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am. J. Psychiatry 157, 1789–1798.
Garavan, H., Pendergrass, J.C., Ross, T.J., Stein, E.A., Risinger, R.C., 2001. Amygdala response to both positively and negatively valenced stimuli. NeuroReport 12, 2779–2783.
Gehring, W.J., Willoughby, A.R., 2002. The medial frontal cortex and the rapid processing of monetary gains and losses. Science 295, 2279–2282.
George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P., Post, R.M., 1995. Brain activity during transient sadness and happiness in healthy women. Am. J. Psychiatry 152, 341–351.
Grant, S., London, E.D., Newlin, D.B., Villemagne, V.L., Liu, X., Contoreggi, C., Phillips, R.L., Kimes, A., Margolin, A., 1996. Activation of memory circuits during cue-elicited cocaine craving. Proc. Natl. Acad. Sci. 93, 12040–12045.
Hamann, S., Mao, H., 2002. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. NeuroReport 13, 15–19.
Hamann, S.B., Ely, T.D., Hoffman, J.M., Kilts, C.D., 2002. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. Psychol. Sci. 13, 135–141.
Harmon-Jones, E., Allen, J.J.B., 1997. Behavioral activation sensitivity and resting frontal EEG asymmetry: covariation of putative indicators related to risk for mood disorders. J. Abnorm. Psychology 106, 159–163.
Heller, W., Nitschke, J.B., Miller, G.A., 1998. Lateralization in emotion and emotional disorders. Curr. Dir. Psychol. Sci. 7, 26–32.
Henson, R., Shallice, T., Dolan, R., 2000. Neuroimaging evidence for dissociable forms of repetition priming. Science 287, 1269–1272.
Ikemoto, S., Panksepp, J., 1999. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res. Rev. 31, 6–41.
Jernigan, T.L., Gamst, A.C., Fennema-Notestine, C., Ostergaard, A.L., 2003. More "mapping" in brain mapping: statistical comparison of effects. Hum. Brain Mapp. 19, 90–95.
Kahneman, D., 1999. Objective happiness. In: Kahneman, D., Diener, E., Schwarz, N. (Eds.), Well-Being: The Foundations of Hedonic Psychology. Russell Sage Foundation, New York, pp. 3–25.
Keselman, H.J., 1998. Testing treatment effects in repeated measures designs: an update for psychophysiological researchers. Psychophysiology 35, 470–478.
Ketter, T.A., Andreason, P.J., George, M.S., Lee, C., Gill, D.S., Parekh, P.I., Willis, M.W., Herscovitch, P., Post, R.M., 1996. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. Arch. Gen. Psychiatry 53, 59–69.
Kilts, C.D., Schweitzer, J.B., Quinn, C.K., Gross, R.E., Faber, T.L., Muhammad, F., Ely, T.D., Hoffman, J.M., Drexler, K.P., 2001. Neural activity related to drug craving in cocaine addiction. Arch. Gen. Psychiatry 58, 334–341.
Knutson, B., Westdrop, A., Kaiser, E., Hommer, D., 2000. fMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 12, 20–27.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001a. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21, RC159.
Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001b. Dissociation of reward anticipation and outcome with event-related fMRI. NeuroReport 12, 3683–3687.
Lane, R.D., Reiman, E.M., Bradley, M.M., Lang, P.J., Ahem, G.L., Davidson, R.J., Schwartz, G.E., 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia 35, 1437–1444.
Lane, R.D., Chua, P.M., Dolan, R.J., 1999. Common effects of emotional valence arousal and attention on neural activation during visual processing of pictures. Neuropsychologia 37, 989–997.
Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia, V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35, 199–210.
Leveroni, C.L., Seidenberg, M., Mayer, A.R., Larissa, A.M., Binder, J.R., Rao, S.M., 2002. Neural systems underlying the recognition of familiar and newly learned faces. J. Neurosci. 20, 878–886.
McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. Neuron 38, 339–346.
Miller, A., Tomarken, A.J., 2001. Task-dependent changes in frontal brain asymmetry: effects of incentive cues, outcome expectancies, and motor responses. Psychophysiology 38, 500–511.
O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., Kobal, G., Renner, B., Ahne, G., 2000. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. NeuroReport 11, 893–897.
O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001a. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 4, 95–102.
O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., 2001b. Representation of pleasant and aversive taste in the human brain. J. Neurophysiol. 85, 1315–1321.
O'Doherty, J., Deichman, R., Critchley, H.D., Dolan, R.J., 2002. Neural responses during anticipation of a primary taste reward. Neuron 33, 815–826.

O'Doherty, J., Dayan, P., Friston, K.J., Critchley, H.D., Dolan, R.J., 2003a. Temporal difference models and reward-related learning in the human brain. Neuron 38, 329–337.

O'Doherty, J., Winston, J., Critchley, H., Perrett, D., Burt, D.M., Dolan, R.J., 2003b. Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 41, 147–155.

Paradiso, S., Robinson, R.G., Andreasen, N.C., Downhill, J.E., Davidson, R.J., Kirchner, P.T., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1997. Emotional activation of limbic circuitry in elderly normal subjects in a PET study. Am. J. Psychiatry 154, 384–389.

Paradiso, S., Johnson, D.L., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 1999. Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. Am. J. Psychiatry 156, 1618–1629.

Petrovich, G.D., Gallagher, M., 2003. Amygdala subsystems and control of feeding behavior by learned cues. Ann. N. Y. Acad. Sci. 985, 251–262.

Pochon, J.B., Levy, R., Fossati, P., Lehericy, S., Poline, J.B., Pillon, B., Le Bihan, D., Dubois, B., 2002. The neural system that bridges reward and cognition in humans: an fMRI study. Proc. Natl. Acad. Sci. 99, 5669–5674.

Rogers, R.D., Owen, A.M., Middleton, H.C., Williams, E.J., Pickard, J.D., Sahakian, B.J., Robbins, T.W., 1999. Choosing between small likely rewards and large unlikely rewards activates inferior and orbital prefrontal cortex. J. Neurosci. 19, 9029–9038.

Rolls, E.T., 1999a. The Brain and Emotion. Oxford Univ. Press, New York.

Rolls, E.T., 1999b. The functions of the orbitofrontal cortex. Neurocase: Case Stud. Neuropsychol. Neuropsychiatry Behav. Neurol. 5, 301–312.

Rolls, E.T., 2000. The orbitofrontal cortex and reward. Cereb. Cortex 10, 284–294.

Rossion, B., Schiltz, C., Robaye, L., Pirenne, D., Crommelinck, M., 2001. How does the brain discriminate familiar and unfamiliar faces?: a PET study of face categorical perception. J. Cogn. Neurosci. 13, 1019–1034.

Schneider, F., Grodd, W., Weiss, U., Klose, U., Mayer, K.R., Nagele, T., Gur, R.C., 1997. Functional fMRI reveals left amygdala activation during emotion. Psychiatry Res. 76, 75–82.

Schoenbaum, G., Chiba, A.A., Gallagher, M., 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat. Neurosci. 1, 155–159.

Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1598.

Schultz, W., Tremblay, L., Hollerman, J.R., 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. Cereb. Cortex 10, 272–283.

Servan-Schreiber, D., Perlstein, W.M., Cohen, J.D., Mintun, M., 1998. Selective pharmacological activation of limbic structures in human volunteers: a positron emission tomography study. J. Neuropsychiatry 10, 148–159.

Small, D.M., Zatorre, R.J., Dagher, A., Evans, A.C., Jones-Gotman, M., 2001. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain 124, 1720–1733.

Stein, E.A., Pankiewicz, J., Harsch, H.H., Cho, J., Fuller, S.A., Hoffman, R.G., Hawkins, M., Rao, S.M., Bandettini, P.A., Bloom, A.S., 1998. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. Am. J. Psychiatry 155, 1009–1015.

Sutton, S.K., Davidson, R.J., 1997. Prefrontal brain asymmetry: a biological substrate of the behavioral approach and inhibition systems. Psychol. Sci. 8, 204–210.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers, New York.

Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer, J., Maguire, R.P., Leenders, K.L., 1997. Activation of the human brain by monetary reward. NeuroReport 8, 1225–1228.

Tomarken, A.J., Davidson, R.J., Wheeler, R.E., Doss, R.C., 1992. Individual differences in anterior brain asymmetry and fundamental dimensions of emotion. J. Pers. Soc. Psychol. 62, 676–687.

Urry, H.L., Nitschke, J.B., Dolski, I., Jackson, D.C., Dalton, K.M., Mueller, C.J., Rosenkranzs, M.A., Ryff, C.D., Singer, B.H., Davidson, R.J., in press. Making a life worth living: neural correlates of well-being. Psychol. Sci.

Vasey, M.W., Thayer, J.F., 1987. The continuing problem of false positives in repeated measures ANOVA in psychophysiology: a multivariate solution. Psychophysiology 24, 479–486.

Wexler, B.E., Gottschalk, C.H., Fulbright, R.K., Prohovnik, I., Lacadie, B.J., Rounsaville, B.J., Gore, J.C., 2001. Functional magnetic resonance imaging of cocaine craving. Am. J. Psychiatry 158, 86–95.

Zalla, T., Koechlin, E., Pietrini, P., Basso, G., Aquino, P., Sirigu, A., Grafman, J., 2000. Differential amygdala responses to winning and losing: a functional magnetic resonance imaging study in humans. Eur. J. Neurosci. 12, 764–1770.