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Sabatinelli D, Bradley MM, Lang PJ, Costa VD, Versace F. Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *J Neurophysiol* 98: 1374–1379, 2007. First published June 27, 2007; doi:10.1152/jn.00230.2007. Recent human functional imaging studies have linked the processing of pleasant visual stimuli to activity in mesolimbic reward structures. However, whether the activation is driven specifically by the pleasantness of the stimulus, or by its salience, is unresolved. Here we find in two studies that free viewing of pleasant images of erotic and romantic couples prompts clear, reliable increases in nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) activity, whereas equally arousing (salient) unpleasant images, and neutral pictures, do not. These data suggest that in visual perception, the human NAc and mPFC are specifically reactive to pleasant, rewarding stimuli and are not engaged by unpleasant stimuli, despite high stimulus salience.

INTRODUCTION

Recent functional imaging studies have linked activation of human reward structures, including nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), to the perception of pleasant emotional stimuli, through the presentation of attractive faces (Aharon et al. 2001; O'Doherty et al. 2003), pictures of loved ones (Aron et al. 2005; Bartels and Zeki 2004; Fisher et al. 2005), aesthetic artwork (Kawabata and Zeki 2004), addictive drug cues (David et al. 2005; Siessmeier et al. 2006), and erotica (Ferreti et al. 2005; Hamann et al. 2004; Karama et al. 2002). Although a commonality of the visual stimuli cited above is pleasant valence, other characteristics shared by these stimuli may be associated with activation of the human NAc and mPFC.

Nonrewarding salient stimuli, operationalized as those that are arousing or elicit attention, have also been shown to prompt ventral striatal activity in humans (Zink et al. 2003, 2006) and in the animal model (Horvitz 2000; Salamone 2005). In these studies, ventral striatal activation is associated with innocuous and infrequent distractor stimuli, irrelevant to a central task. Because these salient stimuli are not pleasant, yet generate measurable responses, it is argued that the ventral striatal system is reward nonspecific. From this perspective, salient pleasant and unpleasant picture stimuli would be expected to prompt equivalent ventral striatal activation.

Past work has determined that picture stimuli rated with high emotional intensity, whether pleasant or unpleasant, are associated not only with greater central and peripheral physiological reactivity (Bradley et al. 2003; Cuthbert et al. 2000; Sabatinelli et al. 2005), but also with extended viewing time, delayed secondary reaction time, and interest ratings (Bradley et al. 1999; see Lang and Davis 2006). This pattern holds true despite equivalent perceptual characteristics (e.g., color, brightness, spatial frequency; Junghöfer et al. 2001; Sabatinelli et al. 2005). Thus for the purposes of this study, we consider pleasant and unpleasant picture stimuli normatively rated with high emotional arousal to have greater salience than neutral pictures with low ratings of emotional arousal.

The human NAc has been reported to show graded responses to cues of varying predictive value, such that greater signal change is associated with more reliable signals of reward (Abler et al. 2006; Knutson et al. 2005; Preuschoff et al. 2006). The rated intensity of emotional stimuli is similarly associated with the magnitude of physiological response; e.g., given equally appetitive or aversive pictures, those rated as more intense elicit a stronger physiological response (Bradley et al. 2001a; Cuthbert et al. 1996; Lang et al. 1993; Sabatinelli et al. 2005). Thus pictures rated as more emotionally arousing might be expected to elicit greater reactivity in NAc.

In the present research, we study male and female participants free viewing pictures judged to be pleasant, neutral, and unpleasant. Findings from two separate experiments are reported, an initial study, and a subsequent replication and extension with a new sample of participants. Three issues regarding human reward circuit reactivity are addressed. First, to investigate the reward-nonspecific (or saliency-driven) perspective of mesolimbic function, we determine whether unpleasant pictures activate the NAc and mPFC to the same degree as pleasant pictures. We include mPFC in this examination because it is a dense cortical site of NAc interconnectivity (Ferry et al. 2000; Roberts et al. 2007) and is correlated with NAc activity in human reward studies (Knutson et al. 2003; Rogers et al. 2004). We also examine the sensitivity of NAc to pictures of equal valence, but varying emotional arousal, to explore whether the structure's graded responsivity to abstract reward predictors (Abler et al. 2006; Knutson et al. 2005; Preuschoff et al. 2006) extends to inherently emotion-evoking stimuli. Finally, considering that sex differences in arousal ratings (Bradley et al. 2001b; Janssen et al. 2003), skin conductance (Bradley et al. 2001b), and visual cortical blood oxygen level–dependent (BOLD) signal (Sabatinelli et al. 2004) have been reported in response to both pleasant and unpleasant picture stimuli, possible parallel differences in NAc and mPFC reactivity in men and women are assessed.

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METHODS

Participants and stimuli

Forty-eight introductory psychology students at the University of Florida participated in the research for course credit or $20.00 compensation. All volunteers consented to participate after reading a description of the study, approved by the local human subjects review board. Before entering the bore of the Siemens 3T *Allegra* MR scanner, participants were fitted with earplugs and given a patient-alarm squeezeball. A vacuum pillow, padding, and explicit verbal instruction were used to limit head motion. Four participants' data were unusable due to excessive head motion, resulting in 44 participants (21 male) in the final sample. Two experiments were conducted using the same research design: in Study 1 (22, 11 male) participants viewed a set of 24 picture stimuli; in Study 2 (22, 10 male), participants viewed a set of 30 picture stimuli (subsequently described).

Participants were asked to maintain fixation on a dot at the center of a 7-in. LCD screen mounted directly behind the head (25° visual angle), visible by a coil-mounted mirror (IFIS MR-compatible hardware, Intermagnetics, Latham, NY). After three acclimation trials in which checkerboard stimuli were presented, a short series of picture stimuli were presented in an event-related design. In Study 1, the 24 grayscale picture stimuli chosen from the International Affective Picture System depicted eight exemplars of erotic couples, neutral people, and mutilations. The erotic and mutilation pictures were selected to be equivalent in normative ratings of emotional arousal (Lang et al. 2001). In Study 2, 30 picture stimuli depicted five exemplars of erotic couples, romantic couples (clothed), neutral people, dental scenes, snakes, and threatening people. The picture series followed a 28-min image-collection period, in which an unrelated paradigm was conducted. The five erotic and neutral people exemplars were chosen from the stimuli used in Study 1.

The erotic, snake, and threat scenes were chosen to be equivalent in normative ratings of emotional arousal, and erotic and romantic were chosen to be equivalent in normative ratings of valence, but differ in normative ratings of emotional arousal, with erotic greater. All picture categories were matched for luminance and 90% quality JPEG file size using Adobe Photoshop 7. Each picture was presented for 3 s, followed by a 9 s (12 s in group 2) fixation-only period. Picture order was pseudorandomized, allowing no more than two successive presentations of a stimulus category.

Scanning parameters

Once participants were comfortable inside the bore, an 8-min three-dimensional structural volume was collected. The prescription specified 160 sagittal slices, with 1-mm isotropic voxels in a 256-mm field of view. After structural acquisition, a functional prescription was placed that included 50 coronal slices (2.5 mm thick, 0.5-mm gap), covering the entire cortex in most participants. Image volumes were collected with 3-s temporal resolution and 16-ml voxel size (TR 3 s, TE 30 ms, flip angle 70°, FOV 160 mm, 64 × 64 matrix). Typical functional image acquisition parameters (axial slices ~5 mm thick) are not optimal for investigations of ventral striatal and ventral prefrontal activity because proximity to the nasal sinus cavities leads to excessive susceptibility artifact and thus signal loss (Merboldt et al. 2001).

Data analyses

Each participant's functional time series were mean-intensity adjusted, linearly detrended, high-pass filtered at 0.02 Hz, and smoothed with a 5-mm spatial filter using BrainVoyager QX (www.brainvoyager.com). Trials containing head motion ($<2\%$) were manually excluded from further analyses. Each participant's preprocessed functional activity was coregistered to his or her structural volume, after transformation into standardized Talairach coordinate space (Talairach and Tournoux 1988). Random-effects analyses identified clusters (>100 ml) of voxels showing greater BOLD signal increase during pleasant relative to neutral picture presentations, using a minimum significance threshold of $P < 0.001$ ($t > 3.8$).

Region of interest analyses were conducted using cluster locations revealed in the group analyses. The random-effects contrast maps were relaxed to a threshold of $P < 0.05$, and a 1-cm^3 volume was located at the voxel of most reliable signal change in the group average. This cluster location was then sampled in each participant's standardized volume, and the peak of this time course (6 s after stimulus onset) was exported for ANOVA analyses including gender and picture category as factors.

RESULTS

Volume analysis

A random-effects ANOVA of the Study 1 average volume identified significant clusters of voxels with greater BOLD signal change in response to erotica relative to neutral people pictures. As shown in Fig. 1, reliable activation was found in NAc (*A*; ±10, 9, −2) and mPFC (*C*; −5, 41, 5). The event-related time course of group-averaged BOLD signal change in these clusters is shown for each picture category in Fig. 1, *B* and *D*, and indicates a selective increase in activity elicited by erotic pictures, but no increase over baseline after presentation of neutral people or mutilation pictures. No significant difference in NAc or

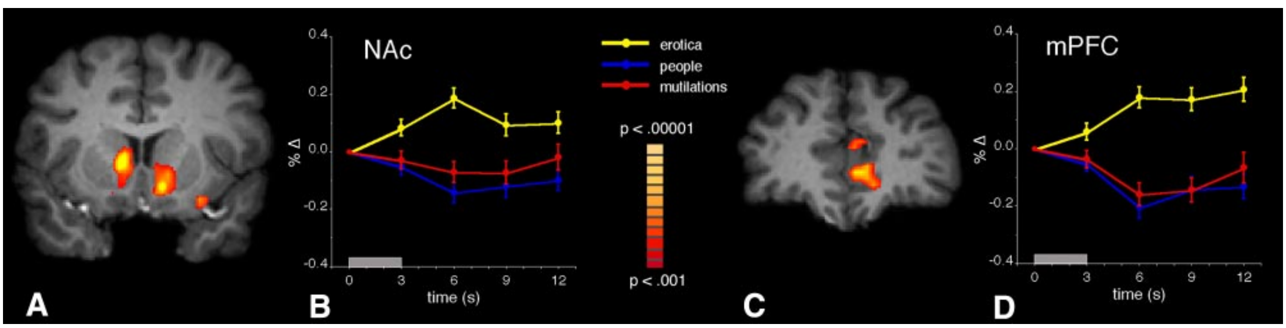

FIG. 1. Study 1: functional activity during erotic picture processing, relative to neutral people pictures. Random-effects analyses reveal bilateral nucleus accumbens (*A*; ±10, 9, −2) and medial prefrontal cortex (*C*; −5, 41, 5) activation that is greater during erotic relative to neutral picture presentations. Event-related time courses of percentage blood oxygenated level–dependent (BOLD) signal change in nucleus accumbens (NAc, *B*) and medial prefrontal cortex (mPFC, *D*) reveal that, in contrast to the response to erotic pictures (yellow), mutilation pictures (red) did not prompt a signal increase and did not differ from activity prompted by neutral people pictures (blue).

mPFC activity was found in contrasts of mutilation and neutral people picture presentations.

Consistent with the Study 1 data, a random-effects ANOVA of the Study 2 average volume identified clusters of voxels in NAc (Fig. 2*A*: ±4, 2, −3) and mPFC (Fig. 2*C*; −4, 39, 4) with greater BOLD signal change during erotic and romantic relative to the least-arousing picture contents (i.e., neutral people and dental). The event-related time course of average signal change is shown for each picture category in Fig. 2, *B* and *D*, illustrating a selective increase in activity after erotic and romantic pictures, but no increase over baseline after presentation of neutral people, dental, snake, or threatening pictures. No significant activity in NAc or mPFC was found in contrasts of more arousing aversive contents (snakes, human threat) and less-arousing picture presentations.

Region of interest analyses

The modulation of Study 1 NAc activity by picture content was reliable in the individually sampled analysis of peak BOLD signal change [$F(2,40) = 32.48$, $P < 0.001$] and consistent across men and women [Content × Gender: $F(2,40) = 1.93$, ns]. Unpleasant and neutral pictures did not elicit differential BOLD signal change in NAc [$F(1,20) = 1.62$, ns]. A similar pattern of signal change was found for peak mPFC activity, where signal change was reliably modulated by picture content [$F(2,40) = 28.47$, $P < 0.001$] and did not interact with gender [$F(2,40) < 1$, ns]. As in NAc, unpleasant and neutral pictures elicited equivalent reactivity in mPFC [$F(1,20) = 1.28$, ns] Table 1.

The modulation of Study 2 NAc activity by picture category was reliable in the individually sampled analysis of peak BOLD signal change [$F(5,100) = 6.32$, $P < 0.001$] and consistent across men and women [Category × Gender: $F(5,100) < 1$, ns]. Unpleasant (snake and threat) and neutral (people and dental) pictures did not elicit differential BOLD signal change in NAc [$F(1,20) < 1$, ns]. A similar pattern of signal change was found for peak mPFC activity, in which signal change was reliably modulated by picture category [$F(5,100) = 8.62$, $P < 0.001$] and did not interact with gender [$F(5,100) = 1.09$, ns]. As in NAc, unpleasant and neutral pictures elicited equivalent reactivity in mPFC [$F(1,20) < 1$, ns] Table 2.

DISCUSSION

Pleasant picture perception was associated with highly reliable increases in NAc and mPFC BOLD signal. This activation is unlikely to be a result of picture salience because images of horrific injuries, threatening snakes, or aggressive people did not elicit signal increases, nor did activity in primary visual cortex differ across picture categories. The clear distinction between NAc and mPFC activity elicited by pleasant pictures and all other picture categories was evident despite a brief presentation series of 24 to 30 total trials. Previous studies with virtually identical stimuli have found strong indications of orienting and novelty responses to aversive pictures, including self-determined viewing time (Lang et al. 1993), skin conductance (Bradley et al. 2001), and the electrocortical event-related potential (Cuthbert et al. 2000; Sabatinelli et al. 2007). Therefore these data do not support the perspective that human ventral striatal reactivity is driven by salience, rather than reward. Selective activation of the NAc and mPFC to pleasant visual stimuli (a valence effect) contrasts with reliable BOLD signal increases elicited by both pleasant and unpleasant visual stimuli (an arousal effect) in amygdala (Breiter et al. 1996; Garavan et al. 2001; Sabatinelli et al. 2005), anterior cingulate (Britton et al. 2006; Bush et al. 2000), and inferior temporal visual cortex (Bradley et al. 2003; Sabatinelli et al. 2005; Vuilleumier et al. 2001) and suggests a dedicated role of NAc and mPFC in reward processing.

The magnitude of NAc and mPFC signal did not differ as a function of whether pictures depicted erotic or romantic content, despite clear differences in normative ratings of emotional arousal. These data suggest that during picture perception, the human NAc and mPFC react specifically to stimulus pleasantness, rather than to emotional arousal. This relative insensitivity to the rated arousal of pictures is unlike the patterns of reactivity seen in a variety of peripheral and central physiological measures, including skin conductance and facial electromyography (Bernat et al. 2006; Lang et al. 1993), the modulation of the startle blink reflex (Bradley et al. 2001; Cuthbert et al. 1996), the amplitude of the electrocortical late positive potential (Cuthbert et al. 2000; Schupp et al. 2003), and in BOLD signal change in ventral visual cortex and amygdala (Bradley et al. 2003; Phan et al. 2004; Sabatinelli et al. 2005; Winston et al. 2005). It should be noted that the pleasant stimuli used here—erotic and romantic couples—were variants on a theme of sexual opportunity, one explicit

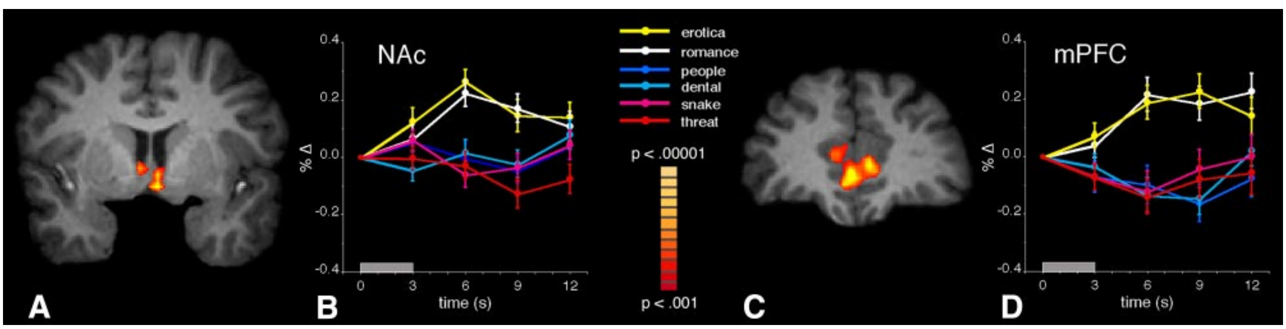

FIG. 2. Study 2: functional activity during erotic and romantic picture processing, relative to neutral people and dental scenes. Random-effects analyses reveal bilateral nucleus accumbens (*A*; ±4, 2, −3) and medial prefrontal cortex (*C*; −4, 39, 4) activation that is greater during erotic and romantic relative to neutral people and dental scene presentations. Event-related time courses of percentage BOLD signal change in NAc (*B*) and mPFC (*D*) reveal that, in contrast to the response to erotic (yellow) and romantic (white) pictures, snake (magenta) and human threat (red) contents did not prompt a signal increase and did not differ from activity prompted by neutral people (blue) and dental scene (light blue) pictures.

TABLE 1. *Region of interest analysis after transformation into standardized Talairach coordinate space for Study 1*

	Pleasant > Neutral					Unpleasant > Neutral			
Region	x	y	z	t(21)	Region	x	y	z	t(21)
Medial prefrontal cortex	−5	41	5	5.87	Amygdala	±21	−6	−11	4.62
Nucleus accumbens	±10	9	−2	7.85	Fusiform gyrus	±34	−69	−10	6.69
Amygdala	±23	−6	−10	6.03	Lateral occipital cortex	±39	−78	−6	4.97
Fusiform gyrus	±39	−60	−7	7.17	Inferior frontal gyrus	±47	15	21	4.37
Lateral occipital cortex	±47	−73	−10	7.11	R intraparietal cortex	28	−72	31	4.92
Inferior frontal gyrus	±44	0	29	5.55	R lingual gyrus	17	−86	−6	4.48
Intraparietal sulcus	±32	−61	54	6.23	Cingulate	−4	−7	33	3.94
Inferior parietal cortex	±57	−29	27	5.38	Postcentral gyrus	±53	−23	37	4.92
Cingulate	8	17	32	5.58	R orbitofrontal cortex	23	33	−7	4.23
Precuneus	−1	−61	40	6.46					
R medial frontal gyrus	26	−6	56	6.65					
L anterior insula	−31	23	4	5.29					

and one implicit. Thus it will be important to reexamine the issue when other pleasant (but nonsexual) stimuli are processed.

No differences between men and women were apparent in subcortical NAc or cortical mPFC, in either sample. It appears that at the level of the mesolimbic reward circuit, both men and women are receptive to this type of pleasant cue. Sex differences seen previously in sensory cortical, peripheral physiological, and self-report measures (Bradley et al. 2001; Costa et al. 2003; Janssen et al. 2003; Karama et al. 2002; Lang et al. 1998; Sabatinelli et al. 2004) and associated sensitivity to variations in emotional arousal may occur in downstream or parallel circuits.

Consistent with previous studies using pleasant visual stimuli (Kawabata and Zeki 2004; O'Doherty et al. 2003), the time course of mPFC activity after pleasant picture onset indicated a clear increase in BOLD signal, in Studies I and II. However, neutral and unpleasant picture stimuli apparently evoke a decrease in mPFC BOLD signal, relative to prepicture baseline. In fact, tests of mPFC signal change reveal reliable decreases in signal intensity after neutral and unpleasant pictures in Study 1 [$F(1,21) = 29.30$, $P < 0.001$] and Study 2 [$F(1,21) = 8.81$, $P < 0.01$]. Although the nature of BOLD signal decrease is less well understood than BOLD increase, and may reflect an interruption of ongoing "default" activity (Gusnard et al. 2001), this pattern of reactivity in mPFC may be a result of an unmet expectation of a pleasant picture (reward) presentation (Knutson et al. 2003; Rogers et al. 2004; Schultz 1998), similar to responses seen in conditioning studies in which predicted rewarding unconditioned stimuli fail to appear (Abler et al. 2006; Pessiglione et al. 2006). Clearly the possibility of decreasing BOLD signal as a function of unmet reward delivery will require more focused research designs.

In summary, the human NAc and mPFC are selectively reactive to pleasant, relative to neutral or unpleasant, picture contents. Furthermore, the magnitude of BOLD signal was determined specifically by the emotional valence of the pictures and not by arousal. That is, highly arousing erotic pictures could not be distinguished from moderately arousing romantic pictures, nor were differences found among the unpleasant picture contents, suggesting that unlike many other neural structures studied in imaging research, the NAc and mPFC are sensitive particularly to picture pleasantness and not to emotional intensity. Finally, these effects appear to be gender general because no difference between men and women was found in the substantial samples of participants studied in two experiments. Overall, these data suggest that activation of the human mesolimbic reward system (i.e., NAc and mPFC) is not enhanced by the salience (arousal, attention capture) of visual scene contents during free viewing, but is specifically a reaction to image pleasantness.

GRANTS

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TABLE 2. *Region of interest analysis after transformation into standardized Talairach coordinate space for Study 2*

	Pleasant > Neutral					Unpleasant > Neutral			
Region	x	y	z	t(21)	Region	x	y	z	t(21)
Medial prefrontal cortex	−4	39	4	7.99	L amygdala	−22	−5	−18	4.41
Nucleus accumbens	±4	2	−3	6.35	Fusiform gyrus	±37	−69	−5	4.91
L amygdala	−20	−8	−8	4.17	Lateral occipital cortex	36	−77	−11	4.31
Fusiform gyrus	±42	−56	−20	4.77	Inferior frontal gyrus	−29	12	−13	5.34
Lateral occipital cortex	±46	−68	−9	5.21	Precuneus	8	−61	10	4.09
Inferior frontal gyrus	±23	15	−9	6.17	Cingulate	9	−13	38	4.15
Precuneus	5	−61	27	5.32	Cuneus	4	−83	19	5.07
Cingulate	1	−14	37	5.08	Anterior cingulate	1	23	22	4.02
Intraparietal sulcus	30	−53	55	3.96					
Precentral gyrus	±28	−10	49	5.27					

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