BRIEF COMMUNICATION

Hunger Selectively Modulates Corticolimbic Activation to Food Stimuli in Humans

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Functional magnetic resonance imaging (fMRI) was used to determine whether visual responses to food in the human amygdala and related corticolimbic structures would be selectively altered by changes in states of hunger. Participants viewed images of motivationally relevant (food) and motivationally irrelevant (tool) objects while undergoing fMRI in alternately hungry and satiated conditions. Food-related visual stimuli elicited greater responses in the amygdala, parahippocampal gyrus, and anterior fusiform gyrus when participants were in a hungry state relative to a satiated state. The state-dependent activation of these brain structures did not generalize to the motivationally irrelevant objects. These results support the hypothesis that the amygdala and associated inferotemporal regions are involved in the integration of subjective interoceptive states with relevant sensory cues processed along the ventral visual stream.

The brain's limited capacity for handling information necessitates the selective allocation of processing resources to stimuli that are relevant to current drives and motivational needs. How the brain assigns salience to environmental cues related to relevant events has yet to be fully understood. The amygdala may play an important role in this process because of its neural connections, which link interoceptive information with information regarding sensory events in the external world (Amaral, Price, Pitkänen, & Carmichael, 1992; Herzog & Van Hoesen, 1976). Although there is support for this function of the amygdala in nonhuman animals, the evidence is more tentative in the human brain.

Animal studies have documented that the amygdala and associated limbic forebrain regions play a crucial role in the coordi-

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nation of appetitive behaviors. Information regarding the perceptual features of food objects processed along the ventral visual stream is associated with other aspects of food quality, such as flavor, within the rhinal cortex (Parker & Gaffan, 1998), an area with dense projections to the amygdala. Amygdala connections with frontostriatal pathways, in turn, regulate response selection and goal attainment on the basis of the incentive value of sensory stimuli (Rolls, 1996; Robbins & Everitt, 1996). In early research, the constellation of behavioral changes in monkeys after an amygdalectomy, such as indiscriminate oral sampling of nonfood and food items and emotional lability (Aggleton & Passingham, 1982; Klüver & Bucy, 1939), had been attributed to a disconnection of visual sensory information from interoceptive cues that signal the motivational relevance of objects (Downer, 1961; Geschwind, 1965). More recent studies of monkeys with bilateral excitotoxic amygdala lesions have confirmed some of these effects, including altered food preferences (Murray, Gaffan, & Flint, 1996) and changes in socioemotional reactivity (Meunier, Bachevalier, Murray, Málková, & Mishkin, 1999).

Excitotoxic amygdala lesions also affect the efficient modulation of food choice by recent food intake. When a positive reinforcer is devalued by selective satiation immediately prior to testing, amygdalectomized monkeys will not alter their choice behavior away from test items paired with that reinforcer (Málková, Gaffan, & Murray, 1997). Similar deficits in reinforcer devaluation adaptation are found in rats with neurotoxic lesions to the basolateral amygdala or orbitofrontal cortex (Gallagher, McMahan, & Schoenbaum, 1999; Hatfield, Han, Conley, Gallagher, & Holland, 1996), and in monkeys following crossed unilateral lesions of the amygdala and orbitofrontal

cortex (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000). These limbic regions thus constitute core nodes of a neural circuit controlling alterations of appetitive behavior by recent ingestive input.

Methodological obstacles have interfered with the ability to determine whether sensory-motivational integration is a property of analogous limbic forebrain regions in humans. Although components of the Klüver–Bucy syndrome can be seen in patients with amygdala lesions (Aggleton, 1993), these patients typically sustain additional damage to frontotemporal neocortex and the hypothalamus. Seizure activity and electrical stimulation in the amygdala of epileptic patients can result in sensory hallucinations, visceral sensations, and evoked emotions (Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982), but these phenomenological changes are not necessarily related to motivational states. Moreover, it has been argued that many motivational functions of the amygdala have been subsumed by the orbitofrontal cortex during evolution, and that this evolutionary shift allows more flexible representations of changes in reinforcement value (Rolls, 1996).

We used whole-brain functional magnetic resonance imaging (fMRI) to assess whether variations in states of hunger would selectively modulate the response of the human amygdala and anatomically related corticolimbic structures to appetitive visual stimuli. Participants viewed images of motivationally relevant (food), motivationally irrelevant (tools), and Gaussian-blurred objects while undergoing fMRI alternately in a hungry and then a satiated state (hungry–satiated group). To control for habituation effects, we scanned an additional group of participants while in a satiated state both times (satiated–satiated group). This experimental design enabled us to test the specificity of the influence of motivational state on visual information processing. Our results suggest that the human amygdala and inferotemporal cortex modulate their responses to sensory events in a manner than reflects their real-time motivational valence.

Method

Participants

Seventeen healthy right-handed adults (9 men, 8 women; mean age = 29, range = 19–44 years) were paid to participate in the study. None of the participants reported a history of psychiatric or neurologic illness. All participants provided informed consent to volunteer in the experiment in accordance with Northwestern University's Institutional Review Board guidelines.

Procedure

Participants in the hungry–satiated group ($n = 9$; 5 men, 4 women) viewed colored images of food, tools, and Gaussian-blurred objects while undergoing fMRI initially in a hungry state and then in a satiated state. Participants were instructed not to eat food for at least 8 hr prior to the imaging session, but were not given any additional information regarding the experimental hypothesis. To reduce unintended influences of circadian rhythms and to increase the saliency of the motivational manipulation, we scanned the participants at a time of day (1700–2000) when a meal is typically ingested. All participants complied with the instructions and reported feeling hungry at the time of testing. To ensure that participants attended to the stimuli during the imaging session, we instructed them to press a button whenever one of the objects blinked. Stimuli blinked on approximately 20% of the trials, divided evenly across the stimulus cate-

gories, by interposing a 100-ms blank interval in the middle of the stimulus presentation (stimulus duration = 3.5 s, interstimulus interval = 0.5 s). All food and tool stimuli were obtained from commercially available CD-ROMs and were formatted to the same resolution and approximate size. An additional object category consisted of a subset of the food and tool images that were Gaussian-blurred so that the objects were not identifiable. These stimuli were included only as a low-level baseline in the event that direct comparison of food and tool items did not yield category-specific activations.

After the initial set of functional and anatomic scans, participants were removed from the magnet and were fed a meal of their choice. Approximately 1 hr later, the experiment was repeated while participants were in a satiated condition. Because amygdala activity habituates to repeated exemplars of the same emotional category (Breiter et al., 1996; Büchel, Morris, Dolan, & Friston, 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Whalen et al., 1998), novel stimuli were introduced in the second testing session, and the stimulus sequence was counterbalanced across participants.

As an additional control over potential habituation effects across testing sessions, a follow-up study was conducted on a second group of participants ($n = 8$; 4 men, 4 women) by using the identical procedure, except that they were fed a meal immediately prior to the first imaging session (satiated–satiated group). This control group was run at the same time of day as the original group and spent an equivalent amount of time out of the magnet between scans, but they were satiated during both testing sessions.

Imaging Parameters and Data Analysis

Imaging was conducted on a 1.5T Siemens Vision scanner (Siemens, Erlangen, Germany) equipped with whole-body gradients and a quadrature head coil. Visual stimuli were backprojected into the scanner room by using an active-matrix LCD projector (Proxima, San Diego, CA) and a custom designed, nonmagnetic rear projection screen. Participants' heads were immobilized with a vacuum pillow (Bionix, Toledo, OH) and restraint calipers built into the head coil, which helped to minimize head movement to ≤ 1 mm in any direction during the testing session (Parrish et al., 1998). The mean maximum motion-correction estimates for the participants in this study were 0.69 mm (hungry–satiated group) and 0.87 mm (satiated–satiated group). Single-shot echoplanar fMRI scans were acquired in 32 contiguous slices parallel to the anterior commissure–posterior commissure line (repetition time/echo time [TR/TE] = 4350/40 ms, flip angle = 90°, field of view [FOV] = 220 mm, matrix = 64 × 64, slice thickness = 4 mm, in-plane resolution = 3.44 × 3.44 mm). Four dummy scans were taken at the beginning of each functional run to decrease the effect of nonsteady state longitudinal magnetization. T1-weighted anatomic images were acquired with a 3-D FLASH sequence (TR/TE = 15/6 ms, flip angle = 20°, FOV = 220 mm, matrix = 256 × 256, slice thickness = 1 mm). Each functional run consisted of 120 scans. Two functional and one anatomic sequence were run in each testing session.

The fMRI data were analyzed with SPM96 (Wellcome Department of Cognitive Neurology, London, UK). All functional images were realigned to the image taken proximate to the anatomic study by using affine transformation routines built into SPM96. The realigned scans were coregistered to the participant's anatomic scan obtained within each session and normalized to SPM96's template image, which conforms to the space defined by the Montreal Neurologic Institute and closely approximates Talairach and Tournoux's (1988) stereotaxic atlas. The functional data were smoothed with a 7-mm isotropic Gaussian kernel prior to statistical analysis. Statistical contrasts were set up by using the general linear model implemented in SPM96 to calculate voxelwise signal differences between the conditions of interest.

We used a fixed-effects model to assess the influence of motivational state on visual responses to food within subjects. Specifically, a double-subtraction procedure contrasted food-related versus tool-related activation

in the hungry state relative to the satiated state, that is, (food–tool) hungry minus (food–tool) satiated. To ensure that the brain regions in the double-subtraction analysis reflected positive activations to food in the hungry condition and not deactivations to tools in the satiated condition, we masked the contrasts (mask threshold = $p < .05$) by the main effect of stimulus category in the hungry state, that is, (food–tool) hungry (see LaBar, Gitelman, Parrish, & Mesulam, 1999, for details). This procedure is statistically equivalent to a motivational state by stimulus category within-subject interaction. Significant interactions were queried further by examining the effect of motivational state on each stimulus category separately. To identify brain regions that showed significant main effects of stimulus category irrespective of motivational state (e.g., food-specific and tool-specific activations), we conducted separate analyses that conjoined food versus tool and tool versus food contrasts across testing sessions (LaBar et al., 1999; Price & Friston, 1997). Identical analyses were computed for the satiated–satiated group. Food and tool items were also contrasted against the Gaussian-blurred objects as a low-level baseline condition. Because the low-level contrasts yielded similar results, we focused on the direct food versus tool comparisons.

Because of our a priori hypotheses about the role of the ventral visual stream and limbic forebrain in visual responses to food, voxel values in the amygdala, insula, and related cortical regions (inferotemporal cortex and orbitofrontal cortex) were considered significant if the activation survived a statistical threshold of $p < .001$ uncorrected ($Z = 3.09$) in either intensity or spatial extent, and had a minimum cluster size of 3 voxels. Furthermore, we hypothesized tool-specific processing in the occipitotemporal junction, on the basis of previous studies (Martin, Wiggs, Ungerleider, & Haxby, 1996; Tranel, Damasio, & Damasio, 1997). Accordingly, voxels in this region were thresholded similarly. Voxel values in other brain regions were considered significant only if they had a corrected voxelwise $p < .05$, with reference to the whole brain as implemented in SPM96 (Friston, Holmes, & Worsley, 1995; Worsley et al., 1996).

Results

Hungry–Satiated Group

Accuracy levels on the blink detection task were at ceiling (over 90% correct), and reaction times did not differ as a function of motivational state ($p > .05$). As illustrated in Figure 1A, food objects elicited significant responses in the amygdala when participants were in a hungry state relative to a satiated state. Three amygdaloid regions in the group average showed food-related activation that was modulated by hunger state (anterior amygdala, basomedial amygdala, and amygdalohippocampal transition area), but only the basomedial region survived our statistical threshold (see Table 1 and Figure 1A). The state effects on amygdala responses did not generalize to the tool stimuli. Follow-up analyses confirmed that activation in the amygdala was found only in response to food when participants were hungry—activation was not observed in response to food items when participants were satiated, and no significant amygdala activation was observed to tools in either motivational state. Although the amygdala responses were left sided in the group-average, inspection of individual participants' data revealed bilateral activation (see Figure 1C).

Two additional brain areas showed food-related activity that significantly interacted with motivational state—the parahippocampal gyrus and anterior fusiform gyrus (see Figure 1A and Table 1). No brain regions were significantly more engaged to food items in the satiated state as compared with the hungry state. Additionally, no brain regions showed hunger modulation of tool-selective responses.

Conjunction analyses revealed tool-specific activation in the occipitotemporal junction bilaterally and food-specific activation in the insula and extrastriate cortex bilaterally. These category-specific regions, which were not modulated as a function of hunger state, are summarized in Table 1 and Figure 1A.

Satiated–Satiated Group

As in the hungry–satiated group, accuracy levels on the blink detection task were at ceiling (over 90% correct), and reaction times did not differ as a function of testing session ($p > .05$). Further analyses showed no significant interactions between testing sessions and activations in the food versus tool contrast. In particular, no significant amygdaloid responses to food stimuli were evident in the double-subtraction or post hoc analyses at the group level or in individual participants. These results suggest that the interactions observed in the hungry–satiated group were related to the motivational state of the participants and not to habituation effects over testing sessions.

The conjunction analysis showed tool-specific activation in the occipitotemporal junction bilaterally and food-specific activation in the extrastriate cortex bilaterally. Neither of these varied as a function of motivational state. The findings from the satiated–satiated group are summarized in Figure 1B and Table 1.

Intrasubject Reliability of Amygdala Activation

To provide an additional control over habituation and novelty effects and to assess the intrasubject reliability of the amygdala activation, we retested 1 male participant from the hungry–satiated group who exhibited robust amygdala activity to food in the hungry state. This participant was retested using the identical paradigm approximately 1 month after the initial session. The results showed significant amygdala activation at retest in the Motivational State × Stimulus Category interaction (Figure 1C).

Discussion

This study shows that visual responses to food stimuli in the human amygdala, parahippocampal gyrus, and anterior fusiform gyrus are selectively modulated in a manner that reflects their current reinforcing value to the subject. These regions may function to regulate goal-oriented behaviors by signaling sensory cues that are relevant to the motivational needs of the organism. The extensive neural connections of the amygdala with sensory association cortex, viscero-autonomic pathways, and the hypothalamus places it in a pivotal position for integrating representations of primary reinforcers with interoceptive states.

One of the most important prerequisites for adaptive behavior is the ability to dynamically reallocate processing resources to behaviorally relevant events. Through its pattern of neural connectivity, the amygdala is ideally suited to subserve this function and provides a critical gateway linking visceral state with sensory information. In particular, the feedback projections from the amygdala to visual association cortices could be used to gate the neural impact of visual stimuli. This study raised the possibility that hunger states can influence visual responses to food stimuli in the fusiform and parahippocampal gyri, perhaps through the mediation of the amygdala. Morris et al. (1998) also found regions of the
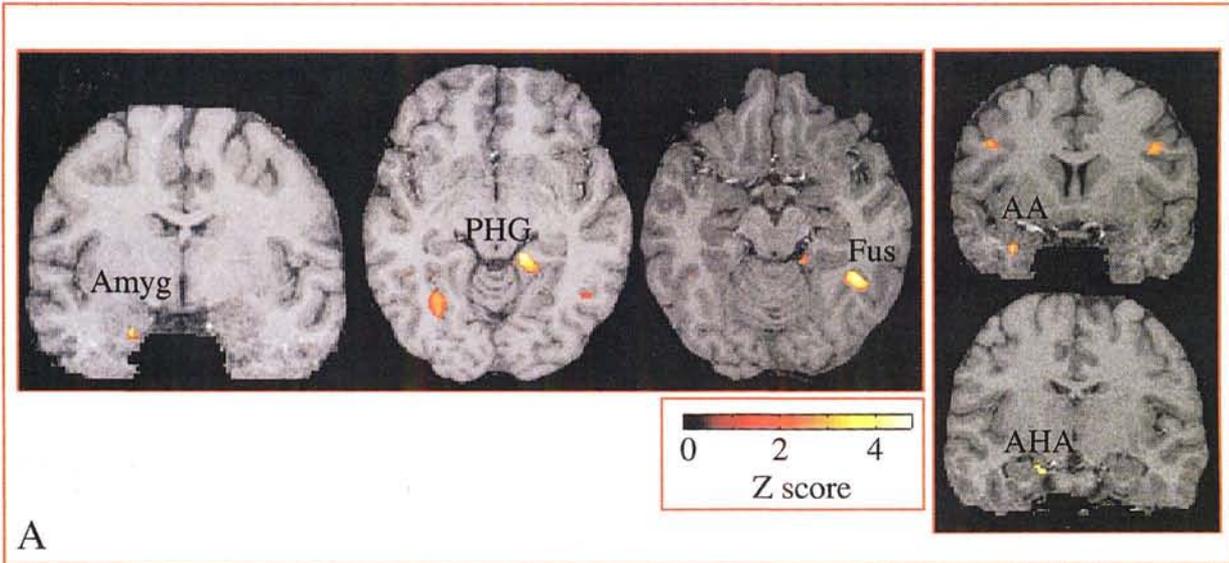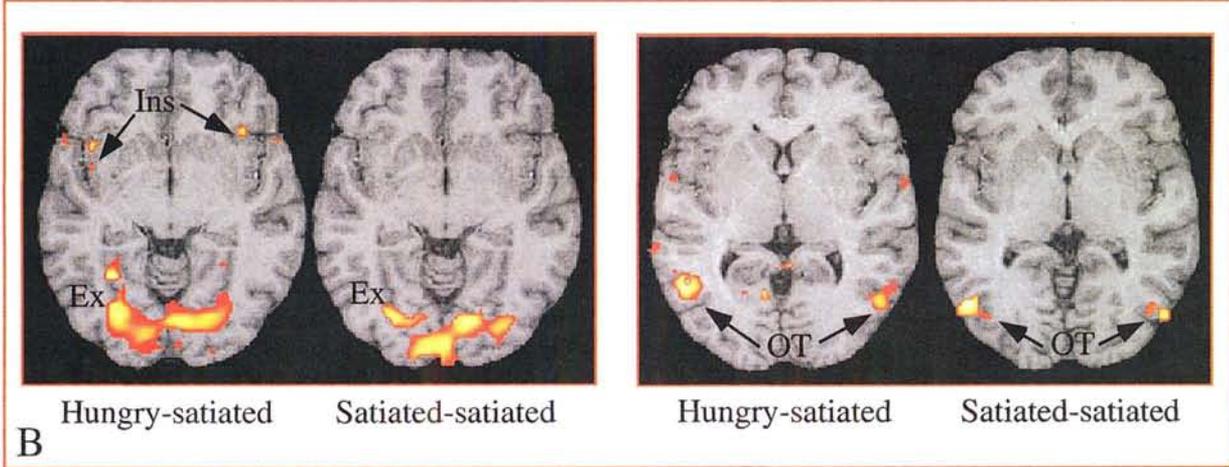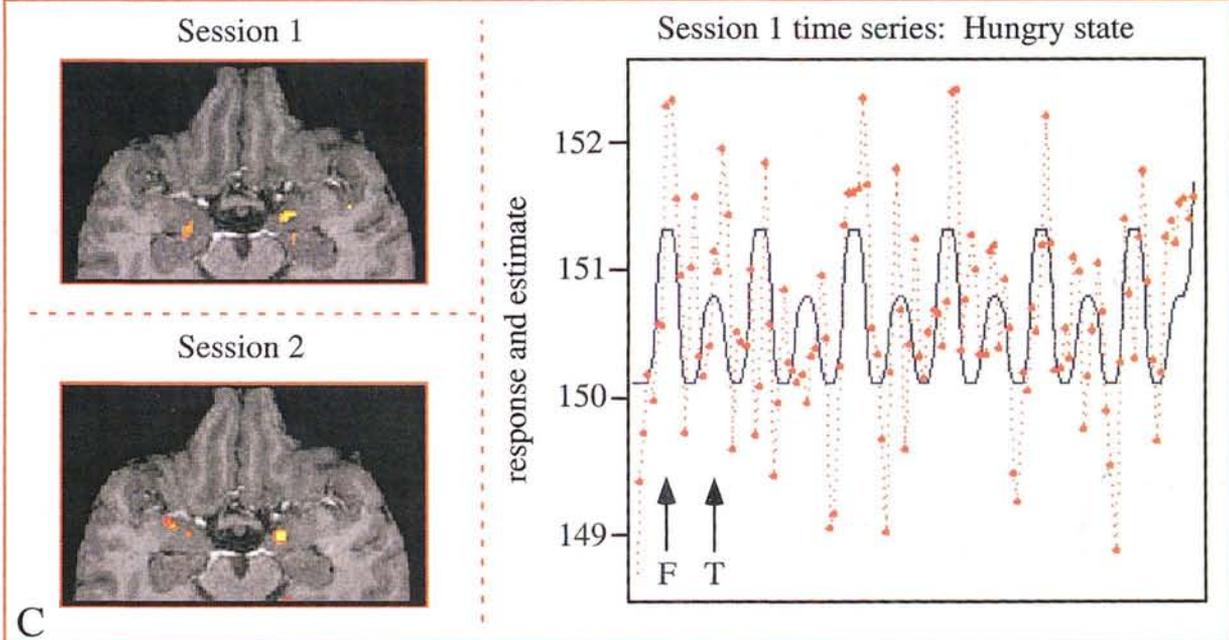
Table 1
Brain Activation Patterns in the Hungry–Satiated and Satiated–Satiated Groups

Group and brain region	Stereotactic coordinates	Maximum Z score	Participant prevalence[a]
Double subtraction analysis: Hunger-modulated food-selective regions			
Hungry–satiated			
Parahippocampal gyrus	18, −36, −12	4.11	2/9 (22)
Fusiform gyrus	45, −48, −21	3.73	7/9 (78)
Amygdala	−21, −3, −27	3.46	2/9 (22)
	−15, −12, 24	2.89[b]	
	−33, 6, −30	2.84[b]	
Satiated–satiated	—	—	—
Conjunction analysis: Food-selective regions			
Hungry–satiated			
Extrastriate cortex	−36, −72, −21	6.97	8/9 (89)
Insula	42, 24, −12	4.38	4/9 (44)
Satiated–satiated			
Extrastriate cortex	−3, −93, 0	5.44	7/8 (88)
Conjunction analysis: Tool-selective regions			
Hungry–satiated			
Occipitotemporal junction	−51, −60, 0	4.64	7/9 (78)
Satiated–satiated			
Occipitotemporal junction	−54, −72, −3	4.60	6/8 (75)

Note. Dashes indicate that no significant activations were found for that group.
[a] Percentages are given in parentheses. [b] Marginally significant at an uncorrected $p < .007$.

ventral visual stream whose responses covaried with amygdala activation to emotional facial expressions. However, neither of these studies proves that amygdalopetal projections underlie the effects. It is possible that each of these temporal lobe areas is modulated by another (as yet unidentified) brain structure or that each region mediates different task-relevant computations. For example, engagement of the parahippocampal gyrus, basal amygdala, or both may relate to incidental mnemonic encoding for salient stimuli, as these regions have been implicated in explicit emotional memory functions in both human and nonhuman studies (Cahill et al., 1995; Cahill & McGaugh, 1998; Hamann, Ely, Grafton, & Kilts, 1999; LaBar & Phelps, 1998). We do not have behavioral evidence, though, that the food items presented in the hungry state were preferentially retained in long-term memory.

It is important to rule out alternative explanations for the state-dependent effects. First, the results were not due to motion artifacts in the hungry group because the participants were able to maintain good head stability, which did not differ from the control group (see Method section). Second, the results are not attributable to

general arousal effects because the influence of motivational state on the activation patterns was regionally- and categorically-specific. Third, previous studies have shown that the amygdala habituates its responsivity when the same exemplars of emotional stimuli are repeated (Breiter et al., 1996; Büchel et al., 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Whalen et al., 1998). To circumvent this issue, we used novel stimuli in the second testing session, counterbalanced the sequence order across participants, added a habituation control group, and demonstrated reliability of the hunger effects in a single participant despite repeated exposure to the identical stimuli. As illustrated in Figure 1C, the amygdala's response to food in the hungry state was relatively stable within the testing session, at least for the 1 participant who was retested.

Studies in nonhuman animals have reported mixed results regarding the sensitivity of neurons in the amygdala and inferotemporal cortex to changes in hunger states. Rolls and colleagues reported that food-related responses were altered by satiation in the hypothalamus and orbitofrontal cortex, but not in the amygdala or

Figure 1 (opposite). Summary of the functional magnetic resonance imaging results. The left side of the brain is depicted on the left side of the images throughout the figure. (A) Left panel: Food-related activation of the basomedial amygdala (Amyg), parahippocampal gyrus (PGH), and anterior fusiform gyrus (Fus) when participants were in a hungry motivational state relative to a satiated motivational state. The group-averaged ($n = 9$) data depict the Object Category × Motivational State interaction superimposed onto a normalized brain space. Right panel: Additional marginally significant activations in the group average included an anterior amygdaloid region (AA) and the amygdala-hippocampal transition area (AHA). (B) Left panel: Category-specific activation to food in the hungry–satiated ($n = 9$) and satiated–satiated ($n = 8$) groups included the extrastriate cortex (Ex) and insula (Ins). Right panel: Category-specific activation to tools in the occipitotemporal junction (OT). These activations were not modulated as a function of motivational state. (C) Left panel: Intrasubject reliability ($n = 1$) of food-related amygdala activation in a hungry state relative to a satiated state across two testing sessions. Right panel: The time series for the most significant voxel in the amygdala follows six repetitions of alternating food (F) and tool (T) blocks, interspersed with Gaussian-blurred objects, while the participant was hungry. Data are from the initial testing session. Vertical axis is labeled in arbitrary units.

inferotemporal cortex of the monkey (Burton, Rolls, & Mora, 1976; Critchley & Rolls, 1996; Rolls, Judge, & Sanghera, 1977; Sanghera, Rolls, & Roper-Hall, 1979; Thorpe, Rolls, & Maddison, 1983). However, Ono, Nishino, and colleagues found that some monkey amygdala neurons alter their responses to food and liquids following changes in palatability and selective satiation, albeit a small percentage (Nishijo, Ono, & Nishino, 1988; Ono & Nishijo, 2000; Ono et al., 1989). Selective cooling of the inferotemporal cortex suppressed the discrimination of amygdala neurons to food items, and selective cooling of the amygdala, in turn, altered hypothalamic responses (Fukuda & Ono, 1993; Ono et al., 1989). Finally, as mentioned earlier, lesions to the basolateral amygdala, orbitofrontal cortex, or their interconnections, render rats and monkeys insensitive to reinforcer devaluation effects (Baxter et al., 2000; Gallagher et al., 1999; Hatfield, et al., 1996; Málková et al., 1997).

The failure to engage the orbitofrontal cortex in the present study is significant given the importance of this region in controlling motivated and appetitive behaviors. One previous study has reported satiety-related changes in human orbitofrontal cortex to the smell of food (O'Doherty et al., 2000). Two possible reasons for the lack of orbitofrontal responses in our study are outlined below. First, the orbitofrontal cortex participates in decision-making processes that link the incentive properties of sensory stimuli to response selection and goal attainment (Baxter et al., 2000; Bechara, Damasio, Tranel, & Damasio, 1997; Gallagher et al., 1999; Rogers et al., 1999; Rolls, 1996; Schoenbaum, Chiba, & Gallagher, 1999). In our task, participants were not required to make decisions or generate actions based on the reinforcing properties of the cues, so we may not have tapped into the relevant functions of this brain area. Second, for technical reasons, we may have had insufficient power to detect signal changes in orbitofrontal cortex. fMRI susceptibility artifacts caused by static field inhomogeneities contribute substantially to the intersubject variability in the vicinity of the amygdala and impair the ability to reliably image the ventromedial prefrontal cortex (LaBar, Parrish, Gitelman, & Mesulam, 2000; Parrish, Gitelman, LaBar, & Mesulam, 2000). Moreover, lateralization of activity in the amygdala may surreptitiously reflect hemispheric asymmetries in signal-to-noise values related to the susceptibility artifacts (LaBar et al., 2000). For this reason, laterality effects in group-averaged fMRI data from the limbic forebrain should be interpreted cautiously. Signal-to-noise factors may also explain why the activation patterns in the amygdala were less prevalent across participants relative to those in the occipitotemporal and fusiform gyri. These issues can be partly mitigated through targeted fMRI studies in limbic regions that use asymmetric spin echo pulse sequences with higher sampling rates (Breiter et al., 1996; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; LaBar, Gatenby, Gore, & Phelps, 1998; Whalen et al., 1998). We did not adopt a targeted approach in this study because we wanted to examine changes across large-scale corticolimbic networks, and because the available spin echo pulse sequences reduced the blood-oxygenated-level-dependent (BOLD) signal by as much as 50% (LaBar & Gatenby, 1996). Such technical limitations underscore a need for new imaging protocols that reduce static inhomogeneity effects in frontolimbic areas while affording maximal BOLD sensitivity and whole-brain coverage.

Several brain areas were characterized by motivationally invariant responses to food or tool stimuli. The occipitotemporal junc-

tion has been implicated as a brain area specialized for the representation of tool objects (Martin et al., 1996; Tranel et al., 1997). This study confirmed tool-selective activation in the occipitotemporal junction in both groups of participants and further showed that the activity was invariant to states of hunger. Food-specific responses were found in the extrastriate cortex and insula bilaterally. The extrastriate activation may reflect categorical differences in the visual properties of food versus tool stimuli or selective attention to the form and color of the food objects. Reasons for the differential insular involvement across participant groups are not well understood (Figure 1B and Table 1). We observed food-related activation of the insula only in the hungry–satiated group, but this activity did not significantly diminish following satiation. The insula activation should have habituated in this group if it was sensitive to modulation by motivational state. One possibility is that hunger-induced elicitation of this region, perhaps through insular connections with the basomedial amygdala (Escobar & Bermúdez-Rattoni, 2000; Mesulam & Mufson, 1985), did not resolve rapidly with satiety. Alternatively, we may have had insufficient statistical power to detect the satiety change or to detect insula activation in the satiated–satiated group. Further research with larger sample sizes will be needed to clarify whether the human insula's responses to food stimuli are invariant to changes in hunger states.

Previous research on the human amygdala has emphasized its role in mediating responses to aversive and fearful stimuli that are inherently arousing (Adolphs, Tranel, Damasio, & Damasio, 1994; Breiter et al., 1996; Büchel et al., 1998; Cahill et al., 1995; Irwin et al., 1996; LaBar, LeDoux, & Phelps, 1998; LaBar, Gatenby, Gore, & Phelps, 1998; Morris et al., 1998; Phelps et al., 1998; Whalen et al., 1998; Zald & Pardo, 1997). By contrast, this study reports a role for the amygdala and inferotemporal cortex in mediating the real-time significance of food stimuli according to the motivational state of the organism. Along with the results of Hamann et al. (1999), our findings extend the known function of the human amygdala to the appetitive domain. In addition, we provide evidence for a broader contribution of these regions to the evaluation of hunger states and their association with motivationally relevant sensory cues processed along the ventral visual stream.

References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994, December 15). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372,* 669–672.

Aggleton, J. P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends in Neurosciences, 16,* 328–333.

Aggleton, J. P., & Passingham, R. E. (1982). An assessment of the reinforcing properties of foods after amygdaloid lesions in rhesus monkeys. *Journal of Comparative and Physiological Psychology, 96,* 71–77.

Amaral, D. G., Price, J. L., Pitkänen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton, (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 1–66). New York: Wiley-Liss.

Baxter, M. G., Parker, A., Lindner, C. C. C., Izquierdo, A. D., & Murray, E. A. (2000). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *Journal of Neuroscience, 20,* 4311–4319.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997, February

28). Deciding advantageously before knowing the advantageous strategy. *Science, 275,* 1293–1294.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., & Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17,* 875–887.

Büchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: An event-related fMRI study. *Neuron, 20,* 947–957.

Burton, M. J., Rolls, E. T., & Mora, F. (1976). Effects of hunger on the responses of neurones in the lateral hypothalamus to the sight and taste of food. *Experimental Neurology, 51,* 668–677.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & McGaugh, J. L. (1995). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences, USA, 93,* 8016–8021.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences, 21,* 294–299.

Critchley, H. D., & Rolls, E. T. (1996). Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *Journal of Neurophysiology, 75,* 1673–1686.

Downer, J. de C. (1961). Changes in visual gnostic function and emotional behavior following unilateral temporal lobe damage in the "split-brain" monkey. *Nature, 191,* 50–51.

Escobar, M. L., & Bermudez-Rattoni, F. (2000). Long-term potentiation in the insular cortex enhances conditioned taste aversion retention. *Brain Research, 852,* 208–212.

Friston, K. J., Holmes, A. P., & Worsley, K. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2,* 189–210.

Fukuda, M., & Ono, T. (1993). Amygdala-hypothalamic control of feeding behavior in monkeys: Single cell responses before and after reversible blockade of temporal cortex or amygdala projections. *Behavioural Brain Research, 55,* 233–241.

Gallagher, M., McMahan, R. W., & Schoenbaum, G. (1999). Orbitofrontal cortex and representation of incentive value in associative learning. *Journal of Neuroscience, 19,* 6610–6614.

Geschwind, N. (1965). The disconnexion syndromes in animals and man. I. *Brain, 88,* 237–294.

Gloor, P., Olivier, A., Quesney, L. F., Andermann, F., & Horowitz, S. (1982). The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Annals of Neurology, 12,* 129–143.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience, 2,* 289–293.

Hatfield, T., Han, J.-S., Conley, M., Gallagher, M., & Holland, P. C. (1996). Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *Journal of Neuroscience, 16,* 5256–5265.

Herzog, A. C., & Van Hoesen, G. W. (1976). Temporal neocortical afferent connections to the amygdala in the rhesus monkey. *Brain Research, 115,* 57–69.

Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., & Turski, P. A. (1996). Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *NeuroReport, 7,* 1765–1769.

Klüver, H., & Bucy, P. C. (1939). Preliminary analysis of functions of the temporal lobes in monkeys. *Archives of Neurology and Psychiatry, 42,* 979–1000.

LaBar, K. S., Gatenby, J. C. (1996). [Comparison of asymmetric spin echo and gradient echo pulse sequences on motor cortex activation during a finger tapping task]. Unpublished raw data.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A.

(1998). Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial study. *Neuron, 20,* 937–945.

LaBar, K. S., Gatenby, J. C., Gore, J. C., & Phelps, E. A. (1998). Role of the amygdala in emotional picture evaluation as revealed by fMRI. *Journal of Cognitive Neuroscience, Suppl S,* 108.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M.-M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: A functional MRI comparison within subjects. *NeuroImage, 10,* 695–704.

LaBar, K. S., Parrish, T. B., Gitelman, D. R., & Mesulam, M.-M. (2000). Impact of signal-to-noise on functional MRI of the amygdala during emotional picture encoding. *NeuroImage, 11,* S231.

LaBar, K. S., Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychological Science, 9,* 490–493.

Málková, L., Gaffan, D., & Murray, E. A. (1997). Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *Journal of Neuroscience, 17,* 6011–6020.

Martin, A., Wiggs, C. L., Ungerleider, L. G., & Haxby, J. V. (1996, February 15). Neural correlates of category-specific knowledge. *Nature, 379,* 649–652.

Mesulam, M.-M., & Mufson, E. J. (1985). The insula of Reil in man and monkey. In A. Peters & E. G. Jones (Eds.), *Cerebral cortex, Vol. 4* (pp. 179–226). New York: Plenum.

Meunier, M., Bachevalier, J., Murray, E. A., Málková, L., & Mishkin, M. (1999). Effects of aspiration versus neurotoxic lesions of the amygdala on emotional responses in monkeys. *European Journal of Neuroscience, 11,* 4403–4418.

Morris, J. S., Friston, K. J., Büchel, C., Frith, C. D., Young, A. W., Calder, A. J., & Dolan, R. J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121,* 47–57.

Murray, E. A., Gaffan, E. A., & Flint, R. W. (1996). Anterior rhinal cortex and amygdala: Dissociation of their contributions to memory and food preference in rhesus monkeys. *Behavioral Neuroscience, 110,* 30–42.

Nishijo, H., Ono, T., & Nishino, H. (1988). Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. *Journal of Neuroscience, 8,* 3570–3583.

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.

Ono, T., & Nishijo, H. (2000). Neurophysiological basis of emotion in primates: Neuronal responses in the monkey amygdala and anterior cingulate cortex. In M. S. Gazzaniga (Ed.), *The new cognitive neurosciences* (pp. 1099–1114). New York: Oxford University Press.

Ono, T., Tamura, R., Nishijo, H., Nakamura, K., & Tabuchi, E. (1989). Contribution of amygdalar and lateral hypothalamic neurons to visual information processing of food and nonfood in monkey. *Physiology & Behavior, 45,* 411–421.

Parker, A., & Gaffan, D. (1998). Lesions of the primate rhinal cortex cause deficits in flavour-visual associative memory. *Behavioural Brain Research, 93,* 99–105.

Parrish, T. B., Gitelman, D. R., Kim, Y.-H., LaBar, K. S., Hallam, D., & Mesulam, M.-M. (1998). Clinical fMRI: Is patient motion really an issue? *NeuroImage, 7,* S560.

Parrish, T. B., Gitelman, D. R., LaBar, K. S., & Mesulam, M.-M. (2000). Impact of signal to noise on functional MRI. *Magnetic Resonance in Medicine, 44,* 925–932.

Phelps, E. A., LaBar, K. S., Anderson, A. K., O'Connor, K. J., Fulbright, R. K., & Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: A case study. *Neurocase, 4,* 527–540.

Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: A new approach to brain activation experiments. *NeuroImage, 5,* 261–270.

Robbins, T. W., & Everitt, B. J. (1996). Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology, 6,* 228–236.

Rogers, R. D., Owen, A. M., Middleton, H. C., Williams, E. J., Pickhard, J. D., Sahakian, B. J., & Robbins, T. W. (1999). Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *Journal of Neuroscience, 20,* 9029–9038.

Rolls, E. T. (1996). The orbitofrontal cortex. *Philosophical Transactions of The Royal Society of London, B,* 1433–1443.

Rolls, E. T., Judge, S. J., & Sanghera, M. (1977). Activity of neurones in the inferotemporal cortex at the alert monkey. *Brain Research, 111,* 53–66.

Sanghera, M. K., Rolls, E. T., & Roper-Hall, A. (1979). Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exploratory Neurology, 63,* 610–626.

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (1999). Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. *Journal of Neuroscience, 19,* 1876–1884.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* New York: Thieme.

Thorpe, S. J., Rolls, E. T., & Maddison, S. (1983). Neuronal activity in the orbitofrontal cortex of the behaving monkey. *Experimental Brain Research, 49,* 93–115.

Tranel, D., Damasio, H., & Damasio, A. R. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia, 35,* 1319–1327.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18,* 411–418.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4,* 58–73.

Zald, D. H., & Pardo, J. V. (1997). Emotion, olfaction, and the human amygdala: Amygdala activation during aversive olfactory stimulation. *Proceedings of the National Academy of Sciences, USA, 94,* 4119–4124.