Neural Responses during Anticipation of a Primary Taste Reward

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Summary

The aim of this study was to determine the brain regions involved in anticipation of a primary taste reward and to compare these regions to those responding to the receipt of a taste reward. Using fMRI, we scanned human subjects who were presented with visual cues that signaled subsequent reinforcement with a pleasant sweet taste (1 M glucose), a moderately unpleasant salt taste (0.2 M saline), or a neutral taste. Expectation of a pleasant taste produced activation in dopaminergic midbrain, posterior dorsal amygdala, striatum, and orbitofrontal cortex (OFC). Apart from OFC, these regions were not activated by reward receipt. The findings indicate that when rewards are predictable, brain regions recruited during expectation are, in part, dissociable from areas responding to reward receipt.

Introduction

It is axiomatic that the goal of most animal behavior is to attain biologically relevant rewards such as food, drink, or sex. A large body of evidence implicates specific brain regions in reward processing, including midbrain dopaminergic nuclei and target areas such as the striatum, as well as orbitofrontal cortex and amygdala (Everitt et al., 1999; Rolls, 2000; Schultz et al., 2000). Two distinct components to reward processing are an anticipatory component, often signaled by the presentation of a cue which reliably signals the subsequent delivery of reward, and a consummatory component relating to reward receipt (Berridge, 1996).

In the animal reward literature, considerable focus has been placed on the role of midbrain dopaminergic neurons arising from the ventral tegmental area (VTA) and substantia nigra (SNigra) in reward (Wise, 1996). It has long been known that animals will work for intracranial self stimulation (ICSS) of these areas (Olds and Olds, 1963). Further, the administration of dopamine agonists increases the rate of responding during ICSS, whereas dopamine antagonists attenuate responding (Gallistel and Karras, 1984; Wise and Munn, 1993). Dopamine release has been reported to increase in the human brain during performance of a video game in which subjects were rewarded for their performance (Koepp et al.,

1998). The precise function of these dopaminergic fibers in reward remains controversial. One hypothesis is that dopamine mediates the hedonic or reward value of a stimulus (Wise, 1985). Alternatively, the dopamine system may be involved in incentive motivation, and could play a role during the anticipation of reward that corresponds to a motivational state of wanting or craving (Berridge, 1996; Berridge and Robinson, 1998). Yet another hypothesis is that dopamine functions as a prediction error during reward learning (Schultz et al., 1997). Evidence consistent with the latter hypothesis comes from single cell neurophysiology recordings in which in the absence of a learned predictive cue, dopamine neurons have been found to respond to the delivery of the reward itself, but after learning, the neurons shift their responses and respond instead to the presentation of a cue which predicts subsequent delivery of a reward (Mirenowicz and Schultz, 1994; Schultz, 1998).

Lesion studies and neurophysiological investigations in nonhuman primates also indicate a role for orbitofrontal cortex, which is itself a target structure of midbrain dopaminergic fibers (Oades and Halliday, 1987) in reward-related processing. Lesions of the orbitofrontal cortex result in altered food preferences in nonhuman primates (Baylis and Gaffan, 1991) and crossed unilateral lesions of the orbitofrontal cortex and amygdala result in impaired reinforcer devaluation, in that the animals were impaired at altering responses to gain access to a reinforcer following a decrease in the reward value of that reinforcer (Baxter et al., 2000). Single-cell neurophysiological recordings indicate that neurons in regions of the orbitofrontal cortex respond to taste, olfactory, and visual stimuli (Rolls, 1997). Some of these neurons are sensitive to the animal's motivational state, in that they respond to the taste or odor of a food when an animal is hungry and decrease their responses when the animal has been fed to satiety (Critchley and Rolls, 1996; Rolls et al., 1989). Neurons have also been found in this region that respond during anticipation of reward (Hikosaka and Watanabe, 2000; Schoenbaum et al., 1998; Thorpe et al., 1983; Tremblay and Schultz, 1999).

Another region implicated in reward is the amygdala. Although there is an emphasis on the role of this region in processing negative and fear-related stimuli and in fear conditioning (Adolphs et al., 1995; LeDoux, 1995), it is also known that amygdala neurons respond to biologically salient rewards such as the taste or sight of food (Ono and Nishijo, 2000; Sanghera et al., 1979; Scott et al., 1993). Further, amygdala lesions cause impairments in reinforcer devaluation (Malkova et al., 1997) as well as disrupting Pavlovian and instrumental appetitive conditioning (Everitt et al., 1999; Parkinson et al., 2000).

Much less is known about how reward is processed in the human brain. Neuroimaging studies of reward-related processing have frequently used monetary reward, which as an abstract secondary reinforcer might be processed differently to primary reinforcers such as food reward (Breiter et al., 2001; Critchley et al., 2001; Delgado et al., 2000; Elliott et al., 2000; Knutson et al., 2000; O'Doherty et al., 2001a; Thut et al., 1997). Investi-

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gation of reward anticipation using money as a reinforcer is complicated by the fact that the receipt of the monetary reward is signaled by verbal or visual feedback which itself constitutes a cue that signals subsequent reimbursement following the imaging experiment. Consequently, it is possible that such paradigms measure stimulus-stimulus learning rather than stimulus-reinforcer learning per se. A number of other studies have reported activations to the presentation of primary reinforcers, where human orbitofrontal cortex has been implicated in representing the reward value of somatosensory as well as olfactory stimuli (Francis et al., 1999; O'Doherty et al., 2000). Activation has also been reported in OFC to receipt of a pleasant taste or food reward (O'Doherty et al., 2001b; Small et al., 1999; Zald et al., 1998). The human amygdala has been found to respond to primary reinforcers, particularly aversive stimuli such as an unpleasant taste, odor, or flavors (Zald et al., 1998; Zald and Pardo, 1997; Small et al., 1997), but also to the receipt of pleasant taste (O'Doherty et al., 2001b). A recent study reported activation of the nucleus accumbens during the unpredictable presentation of food rewards (Berns et al., 2001). However, no study has yet addressed the issue of which brain regions are involved during anticipation of a primary taste reward, particularly where reward is reliably predicted by a sensory cue.

The aim of the present study was to determine which brain areas are involved during anticipation of a pleasant taste reward and to contrast these regions with those involved in responding to the reward itself. Using functional magnetic resonance imaging (fMRI), we measured neural responses while subjects were presented with one of three arbitrary visual stimuli, each of which reliably predicted the subsequent delivery of either a moderately pleasant sweet taste, a moderately unpleasant salty taste, or a neutral control solution (see Figure 1A). In this study, we considered the arrival of a taste in the mouth to constitute the receipt of the reward rather than when the taste was swallowed, though we acknowledge that post-ingestive effects also contribute to the overall reward value of a taste. We used a novel EPI imaging technique designed to maximize the signal from OFC and medial temporal lobes, regions particularly sensitive to susceptibility artifact (Ojemann et al., 1997). We predicted responses in regions known to be involved in reward: the midbrain, striatum, OFC, and amygdala. Given that reward was delivered reliably and predictably throughout, a specific prediction derived from both incentive motivation theory and reward-learning theory is that activation would occur within midbrain dopaminergic nuclei and their target structures to anticipation of taste reward.

Results

Subjective Ratings

Following the scanning sessions, subjects rated the subjective pleasantness of the three taste stimuli on a scale from $+2$ = very pleasant through 0 = neutral to -2 = very unpleasant. The mean pleasantness rating for the glucose (moderately pleasant taste) was $+1.06 \pm 0.17$ (SD); for the salt (moderately aversive taste) -0.83 ± 0.26;

and for the neutral taste 0.125 ± 0.44. (see Figure 1D). There was a significant difference between the ratings as shown by a nonparametric Friedman related samples test ($X^2 = 11.625$, df = 2; $p < 0.005$). Post-hoc Wilcoxon tests revealed that the glucose taste was rated as significantly more pleasant than the neutral and salt tastes and that the salt taste was rated as significantly less pleasant than the neutral taste (each at $p < 0.05$). A Friedman test revealed no significant differences between the perceived intensity of the three tastes.

Neuroimaging Results

Anticipation of Glucose (ANTglc) − Anticipation of Salt (ANTslt)

The ANTglc − ANTslt contrast was performed to reveal areas responding more to anticipation of the pleasant glucose taste than to anticipation of the moderately unpleasant salt taste. This contrast revealed extensive bilateral activation of the ventral tegmental area/substantia nigra, at $p < 0.05$ corrected for small volume (SVC) using a sphere of radius 10 mm centered on the VTA (coordinates 8, -24, -18; peak z = 4.22; and -8, -20, -18; z = 3.74; Figure 2A). To gauge the reproducibility of this activation across subjects, a more stringent statistical test was applied by performing the contrast of ANTglc − ANTslt for each individual subject separately followed by a conjunction analysis across each of the single subjects (Friston et al., 1999). This analysis is sensitive to activation within voxels that show a significant effect in every subject and is thus intrinsically stringent and robust. This conjunction analysis revealed significant effects in left dopaminergic midbrain (coordinates -8, -20, -22; peak z = 4.39; $p < 0.05$ corrected for whole brain; Figure 2B).

Also showing significantly greater effects to anticipation of glucose relative to anticipation of salt was a part of the striatum: right putamen (18, 0, 12; z = 3.58; $p < 0.001$ uncorrected; see Figure 3A). Right putamen also survived a conjunction across subjects (20, 2, 0; z = 3.96; $p < 0.05$ SVC using a 30 cm³ bilateral mask defined over the anatomical boundaries of the striatum). Effects were also found in part of posterior dorsal amygdala bilaterally, adjacent, and superior to the anterior hippocampus (16, -10, -16; peak z = 3.75; -12, -10, -16) and left anterior amygdala (-16, 2, -16; peak z = 3.5) (at $p < 0.05$ corrected for small volume (SVC) using an $\sim$10 cm³ region of interest defined over the anatomical boundaries of bilateral amygdala). The effects in the amygdala did not survive a conjunction across subjects of ANTglc − ANTslt, but an area bordering the right dorsal amygdala did survive a conjunction across subjects of the main effect of ANTglc (18, -6, -10; z = 3.86; $p < 0.05$ SVC; Figure 3B). An effect was also found in the orbitofrontal cortex at $p < 0.001$ in the contrast of (ANTglc − ANTslt) (28, 38, -16; peak z = 3.1). The responses in this region showed evidence of habituation over sessions, as revealed by the contrast of ANTglc − ANTslt restricted to the first two sessions only, masked inclusively by the direct comparison between the 1st and 4th sessions of the ANTglc condition at $p < 0.05$ (i.e., ANTglcsess1 − ANTglcsess4).

Anticipation of Glucose − Anticipation of Neutral

Significant activations were also observed in midbrain dopaminergic nuclei when comparing anticipation of
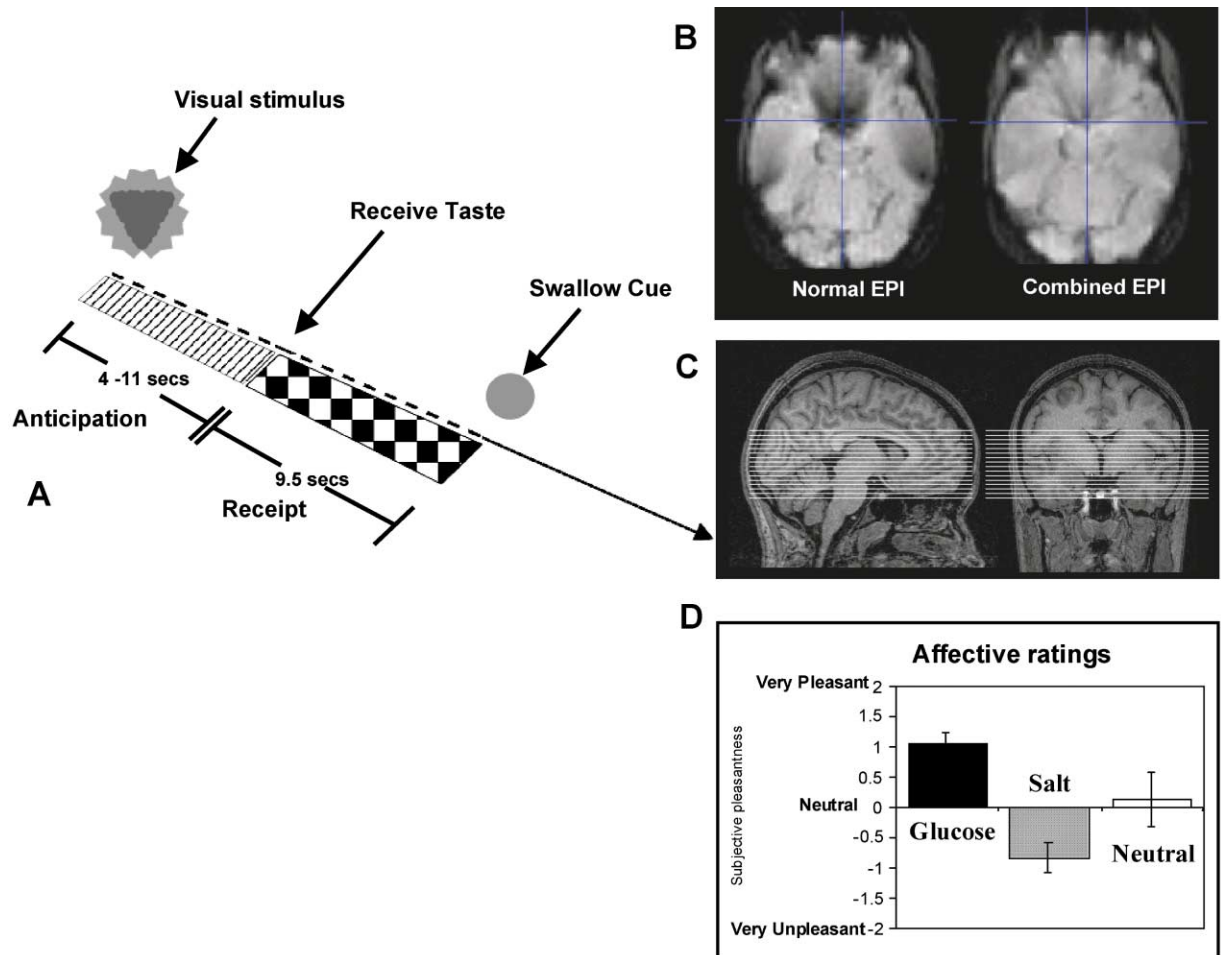
Figure 1. Experimental and Imaging Protocol

(A) The experimental task: presentation of a visual stimulus at the beginning of a trial cues the delivery of 0.5 ml of one of three tastes: glucose, salt, or neutral after a pseudo-random interval of between 4 and 11 s. Once the taste is delivered, swallowing is cued after 9.5 s, and the subsequent trial begins 3 s later. (B) Raw EPI taken from a single subject showing the recovery of signal dropout induced by susceptibility artifact using the combined EPI sequence (relative to a normal EPI). The images shown are from the same subject. (C) Illustration of the area of the brain covered by the 16 axial slices during the functional sequence. (D) The subjective pleasantness ratings provided by the subjects for the three tastes, using a scale ranging from $+2$ = very pleasant, 0 = neutral, through to -2 = very unpleasant.

glucose to anticipation of neutral taste (*ANTneu*) (see Table 1).

Responses were also observed in orbitofrontal cortex when performing a contrast between the ANTglc − ANTneu conditions restricted to the first two sessions alone, masked by the direct comparison between the 1st and 4th sessions of the *ANTglc* condition at $p < 0.05$ (i.e., *ANTglcsess1 − ANTglcsess4*) (Figure 4A).

Anticipation of Glucose − Taste of Glucose

To test whether the above regions were more activated by reward anticipation than by reward receipt (*TSTglc*), the contrast of ANTglc − TSTglc was performed, masking exclusively by *ANTneu − TSTneu* (where *TSTneu* = receipt of neutral taste) at $p < 0.05$ uncorrected. This contrast enabled voxels which were more activated by reward anticipation than by reward receipt to be detected, yet excluding voxels in which there was greater activation to the anticipation of neutral taste than to the receipt of neutral taste. Significant effects in dopaminergic midbrain were again seen in this contrast ($p < 0.05$

SVC). (see Figure 2C; Table 2). An area of ventral striatum (nucleus accumbens) was found to respond significantly more to the anticipation of glucose than to its receipt as identified by the contrast: *ANTglc − TSTglc* masked exclusively by *ANTneu − TSTneu* (12, 2, −2, z = 3.8; $p < 0.001$ uncorrected; Table 1). A part of posterior right amygdala also showed significantly greater activation to the anticipation of glucose than to its receipt (28, −8, −14, z = 3.95; $p < 0.05$ SVC; Figure 3B); the region also survived the conjunction across subjects of the same contrast (at $p < 0.05$ SVC).

Anticipation of Salt Taste − Anticipation of Neutral Taste

In the contrasts of *ANTslt − ANTneu*, no significant effects were observed in predicted areas of interest at $p < 0.001$. For descriptive purposes, we report below threshold activation in left lateral OFC at $p < 0.006$ uncorrected (−38, 46, −4; peak z = 2.49). Outside regions of interest, responses were observed to the anticipation of salt taste in visual cortical areas (see Table 1).
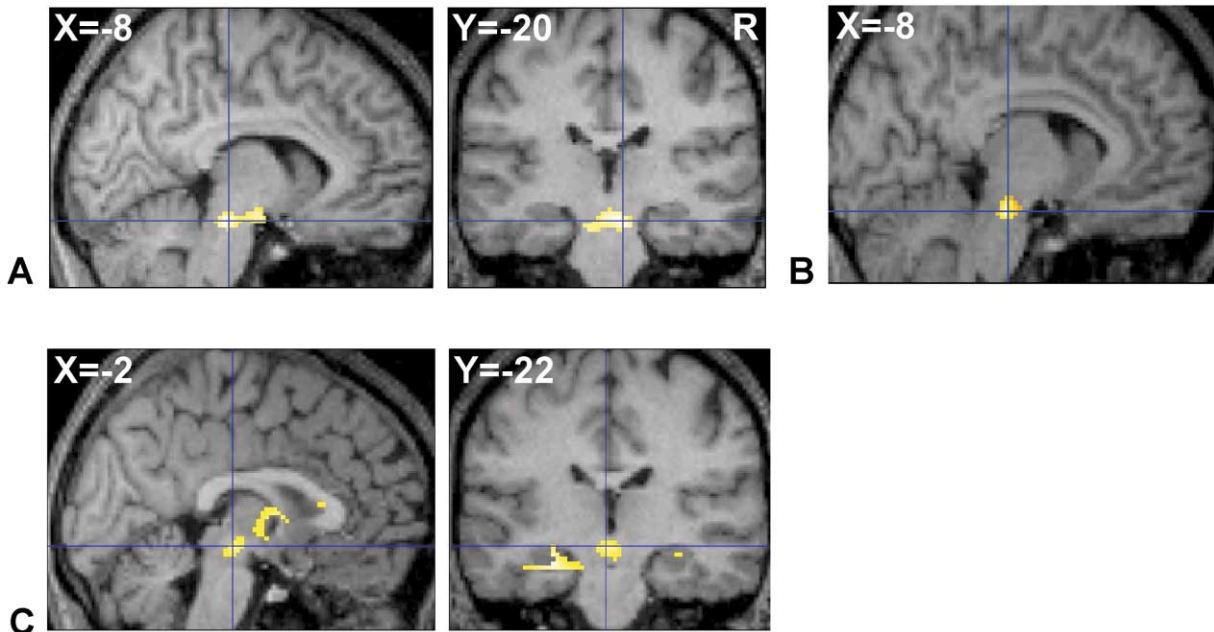
Figure 2. Responses of Midbrain Dopaminergic Nuclei to Anticipation of Pleasant Taste

Areas of dopaminergic midbrain including the ventral tegmental area (VTA) and substantia nigra (SNigra) showing responses to the anticipation of glucose (taste reward).
(A) Comparison between anticipation of glucose and anticipation of salt (*ANTglc − ANTslt*).
(B) The conjunction across subjects of *ANTglc − ANTslt*.
(C) Comparison between anticipation of glucose and receipt of glucose (*ANTglc − TSTglc* masked exclusively by *ANTneu − TSTneu)*.
The threshold is set at p < 0.001 uncorrected for illustration.

Anticipation of Salt − Taste of Salt

The contrast of ANTslt − TSTslt masked exclusively by ANTneu − TSTneu revealed effects in right orbitofrontal cortex at p < 0.001 uncorrected (10, 44, −22, peak z = 3.58).

Main Effect of Taste Receipt

The main effect of taste receipt (summed over the *TSTglc*, *TSTslt*, and *TSTneu* conditions) identified regions responding to the receipt of a taste in the mouth, including somatosensory, tongue, and mouth movement components. This contrast revealed a region of right insula and adjoining frontal operculum responding to taste receipt, most prominently on the right (54, 2, 2; peak z = 6.2; p < 0.05 corrected; see Figure 5A). Effects were also seen in the left insula/operculum at p < 0.001 uncorrected (−58, 10, 2; peak z = 3.59).

Taste of Glucose − Taste of Neutral

The contrast of *TSTglc − TSTneu* revealed a region of dorsal frontal operculum that was more activated by the receipt of taste reward than by the receipt of neutral taste at p < 0.001 (54, 0, 18; peak z = 3.2). No significant effects were observed in OFC to the receipt of pleasant taste at p < 0.001. In order to determine whether habituation may have occurred, the contrast of *TSTglc − TSTneu* pooled over the first two sessions was performed, masked by the difference between the *TSTglc* condition of the 1st and 4th sessions (*TSTglcsess1 − TSTglcsess4)*. The only region to survive this contrast was a region of right OFC (42, 46, −16; peak z = 3.95; p < 0.05 SVC using 60 cm³ OFC mask; Figure 4B). The peak activation was ∼10 mm more lateral to the region

found to respond to the anticipation of glucose (see above).

Taste of Glucose − Anticipation of Glucose

The contrast of *(TSTglc − ANTglc)* exclusively masked by *(TSTneu − ANTneu)* was carried out to identify voxels that showed a greater response to the receipt of glucose than to the anticipation of glucose, yet controlling for nonspecific effects relating to the visual cue presentation or taste receipt. The only region of interest to survive this contrast was a part of right anterior OFC (28, 58, −14; peak z = 3.85; p < 0.05 SVC).

Taste of Salt − Taste of Neutral

The contrast of *(TSTslt − TSTneu)* revealed activation in the dorsal frontal operculum that showed greater activation to the unpleasant taste than to the neutral taste (56, 8, 20; peak z = 4.2; p < 0.001). In addition, activation was found in right OFC, more anteriorly to that found for receipt of pleasant taste (28, 60, −12; peak z = 3.65; p < 0.001). The region did not show habituation during the course of the experiment, tested by a comparison between the 1st and 4th sessions.

Taste of Salt − Taste of Glucose

No areas showed significantly greater responses to the receipt of salt compared to the receipt of glucose, nor to the receipt of glucose compared to the receipt of salt.

Discussion

The goal of this study was to identify brain regions that responded to anticipation of a primary taste reward and to compare these responses to those associated with reward receipt. The finding that dopaminergic midbrain
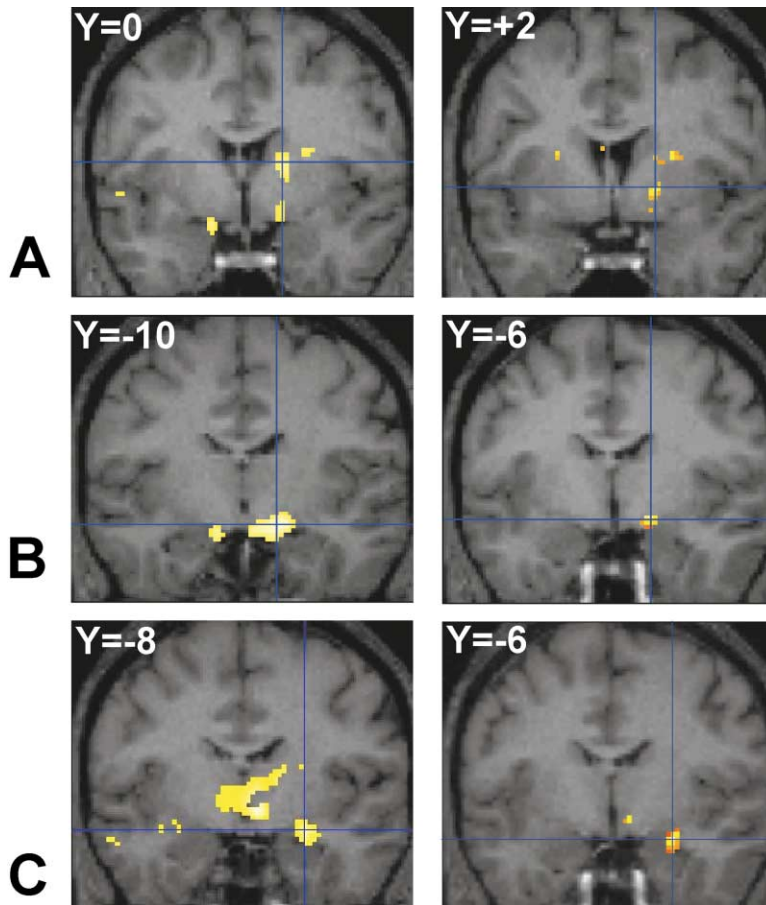
Figure 3. Activation of Striatum and Amygdala during Anticipation of Pleasant Taste

(A) Regions of striatum showing activation to anticipation of glucose relative to the anticipation of salt as revealed by a fixed effects group contrast of ANTglc − ANTslt (left).The results of a conjunction across subjects of this contrast are also shown (right).

(B) a part of the posterior dorsal amygdala and an adjacent area, showing responses to the anticipation of glucose taste relative to the anticipation of salt (left). Also shown is the conjunction across subjects of the main effect of ANTglc revealing activation of a region bordering the amygdala (right).

(C) Results from the ANTglc − TSTglc comparison, indicating that right amygdala as well as right hypothalamus extending anteriorly into ventral striatum (with a separate peak in this region) shows significantly greater responses to the anticipation of taste reward than to its receipt. As in (A) and (B) above, the fixed effects group result (left) and the conjunction across subjects are shown (right). The threshold is set at $p < 0.001$ uncorrected for illustration.

was responsive during anticipation of taste reward is consistent with single-cell neurophysiological studies in nonhuman primates. Such studies report responses in dopamine neurons during the anticipation of food rewards, when associations between a predictive cue and a reinforcer has been learned (Mirenowicz and Schultz, 1994). In this study, reward-related anticipatory responses were also observed in a principle target region of these dopaminergic afferents, namely the striatum (including nucleus accumbens).

The finding that VTA and striatum respond during reward anticipation but not during reward receipt is compatible with two theoretical accounts of the role of dopamine in reward: the reward-learning hypothesis and the incentive motivation theory (Schultz, 1998; Berridge, 1996). It should be noted that the BOLD (blood oxygenation level dependant) imaging technique used in this study is not in itself sensitive to dopamine release. A recent study has indicated that a likely source of the BOLD signal is neural activity relating to afferent inputs as well as local processing within a region (Logothetis et al., 2001). Thus, detection of differential BOLD responses in brain regions such as VTA may reflect afferent inputs and local neural activity within VTA rather than corresponding directly to dopaminergic output.

According to the reward learning hypothesis, dopamine neurons function as a prediction error that signal a discrepancy between the expected delivery of a reward and reward receipt (Schultz et al., 1997). The notion

of prediction error is central to theoretical accounts of reinforcement learning such as the Rescorla-Wagner rule and temporal difference (TD) learning (Rescorla and Wagner, 1972; Sutton and Barto, 1981). Dopamine responses in nonhuman primates have been argued to be consistent with a prediction error in a TD learning implementation, responding to the receipt of a reward when it is not fully predicted, decreasing responses when a predicted reward fails to occur, and responding to the earliest cue which reliably predicts the subsequent reward following learning (Schultz et al., 1997). In the present study, we did not manipulate the predictability of reward, but instead delivered a reward reliably and consistently following presentation of a visual cue. The finding of activation in VTA and striatum to a predictive cue could therefore be compatible with this theory. However, an important caveat is that we used a variable interval between cue presentation and reward delivery. This contrasts with neurophysiological studies by Schultz and colleagues where a fixed interval between the presentation of the reward and the delivery of the cue was used (Schultz, 1998). Furthermore, the TD model used to account for this neurophysiology data incorporates within-trial interval timing to enable the prediction of reward delivery at a fixed time point during the trial, and is thus not directly applicable in the case of the variable intervals used in the present study (Schultz et al., 1997).

The incentive motivation theory also implicates the

Table 1. Regions Responding during Anticipation of Glucose and Salt Tastes

		MNI Coordinates					
		X	Y	Z	Peak Z		Conjunction
Anticipation of Glucose > Anticipation of Neutral (ANTglc − ANTneu)							
Dopaminergic midbrain	Left	−12	−20	−22	3.45	p < 0.001	—
Orbitofrontal cortex[a]	Right	32	46	−6	3.77	p < 0.001	—
Anticipation of Salt > Anticipation of Neutral (ANTslt − ANTneu)							
Orbitofrontal cortex/lateral PFC[b]	Left	−38	46	−4	2.49	p < 0.006	—
Visual cortical areas	Right	22	−80	−2	5.43	p < 0.05wb	—
	Left	−10	−90	0	6.54	p < 0.05wb	Y
Anticipation of Glucose > Anticipation of Salt (ANTglc − ANTslt)							
Dopaminergic midbrain	Right	8	−24	−18	4.21	p < 0.05c	—
	Left	−8	−20	−18	3.74	p < 0.05c	Y
Striatum: putamen	Right	18	0	12	3.57	p < 0.001	Y
Amygdala/adjacent areas	Right	−16	−10	−14	3.86	p < 0.05c	Y[c]
	Left	−12	−10	−16	3.5	p < 0.05c	—
	Left	−16	2	−16	3.5	p < 0.05c	—
Orbitofrontal cortex[a]	Right	28	38	−16	3.55	p < 0.001	Y
Insula	Left	−50	−6	−4	3.42	p < 0.001	—
Anticipation of Glucose > Receipt of Glucose (ANTglc − TSTglc) masked exclusively by (ANTneu − TSTneu)							
Dopaminergic midbrain	Left	−2	−22	−10	3.95	p < 0.05c	Y
Hypothalamus	Right	8	−6	−6	4.49	p < 0.05wb	Y
Striatum: nucleus accumbens	Right	12	2	−2	3.8	p < 0.001	—
Amygdala	Right	28	−8	−14	3.94	p < 0.05c	Y
Hippocampus	Right	22	−14	−18	3.73	p < 0.001	Y
Hippocampus	Left	−28	−24	−16	4.78	p < 0.05wb	Y
Orbitofrontal cortex	Right	24	18	−16	3.5	p < 0.001	—
Anticipation of Salt > Receipt of Salt (ANTslt − TSTslt) masked exclusively by (ANTneu − TSTneu)							
Orbitofrontal cortex	Right	10	44	−22	3.58	p < 0.001	—

[a] Revealed by contrast sensitive to the effects of habituation across sessions (see text).
[b] Reported here for descriptive purposes only.
[c] Conjunction of main effect of ANTglc only.
c—corrected for small volume restricted to region of interest.
wb—corrected for whole brain volume.

dopamine system in reward anticipation, where dopamine neurons are argued to reflect the incentive or motivational value of a future reward, reflected in the degree to which an animal will work for reward, and corresponding to a subjective state of "wanting" (Berridge, 1996). According to this theory, the "wanting" component of reward is dissociable from the "liking" or hedonic aspects evident during reward consumption. Rats with selective dopamine lesions show profound aphagia and will not work to attain food reward, but nevertheless show unaltered "affective" reactions in response to delivery of a pleasant sweet taste (Berridge et al., 1989). In this context, it is of interest that we show that regions responding to the receipt of the reward were at least partially dissociable from regions that responded during reward anticipation.

As expected, activation was observed in primary taste cortex and in OFC during reward receipt. Although the OFC was also found to respond during the anticipation of taste reward, regions responding to anticipation and receipt were ~10 mm apart. Furthermore, in a direct comparison, an area of anterior OFC was found to have significantly greater responses to the receipt of reward. It is known that OFC in nonhuman primates contains

the secondary gustatory cortex, and that some neurons in this region reflect the hedonic or reward value of a food (Rolls et al., 1989). There is also preliminary evidence in humans that parts of OFC represent the reward value of food stimuli (O'Doherty et al., 2000). The finding in the present study of OFC responses during reward anticipation is consistent with extensive data from single cell neurophysiology, in which neurons in this region respond to the presentation of a visual cue which predicts the delivery of a reward (Thorpe et al., 1983), or during a delay period when a reward is expected (Schoenbaum et al., 1998; Tremblay and Schultz, 1999). However, we note that unlike the present study, in some of the above neurophysiological studies, the cue was switched off before the presentation of the reinforcer and so anticipatory responses measured during this period may constitute a different form of anticipatory coding. The habituation of responses in this region over the course of the experiment to both anticipation and reward receipt is notable, especially given that responses did not habituate to the receipt of aversive taste. One possible explanation for this adaptation is that the pleasantness or reward value of the sweet taste may have decreased over the course of the experiment, but clearly
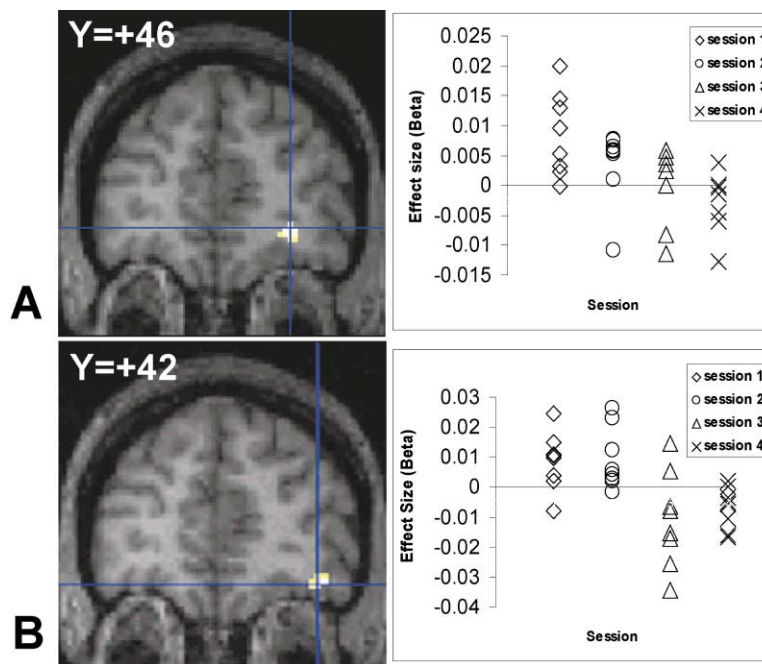
Figure 4. Responses in Orbitofrontal Cortex

Activation in orbitofrontal cortex (on left of figure) which had attenuated by the 4th session during (A) anticipation of glucose as revealed by the ANTglc − ANTneu comparison, and (B) receipt of taste reward as revealed by the TSTglc − TSTneu comparison.

The effect size (β values) for individual subjects across the four sessions are plotted (right) for (A) the ANTglc − ANTneu contrast and (B) the TSTglc − TSTneu contrast. These β values show a decreasing trend in most subjects from session 1 to session 4. (Note: a prominent exception in one subject was a relatively high β value [with respect to the other values] of 0.17 in session 3 in (A) which is treated as an outlier and not plotted on the graph in [A].) The threshold is set at p < 0.001 uncorrected for illustration.

this possibility will need to be evaluated in a subsequent study. However, the results of the present study do suggest that in humans, as in nonhuman primates, orbitofrontal cortex is involved in both anticipatory and consummatory aspects of reward processing.

A part of posterior dorsal amygdala (adjacent to the hippocampus) showed greater responses during anticipation of glucose than anticipation of salt. Given the current emphasis on the role of the amygdala in fear and fear conditioning in the literature (Adolphs et al., 1995; LeDoux, 1995), this finding suggests that the amygdala is also involved in responding to reward. This result is consistent with findings from lesion studies in animals in which amygdala lesions cause marked impairments at both classical and instrumental appetitive conditioning (Everitt et al., 1999; Parkinson et al., 2000). The results described here thus point toward a role for the human amygdala in positive as well as nega-

tive affect. In the present study, responses were only observed in the amygdala during the anticipation of taste reward and not to the receipt of the reward, whereas in a previous study, responses were found in the left amygdala to the receipt of taste reward (1 M glucose) (O'Doherty et al., 2001b). One possible explanation for this difference is that in the previous study, a block design was used, in which the order of delivery of the stimuli was predictable. Thus it is possible that in this earlier study, anticipatory responses occurring just before the presentation of the taste reward also contributed to the observed activation.

A novel aspect of our study is that we measured anticipatory responses to a primary reinforcer, which contrasts with most other studies of reward-learning that have used monetary reward. The latter have used complex probabalistic tasks with varying levels of reward outcome on each trial (Elliott et al., 2000; Delgado et

Table 2. Regions Responding following Receipt of Glucose and Salt Tastes

| | | MNI Coordinates | | | | | |
		X	Y	Z	Peak Z		Conjunction
Receipt of Glucose > Receipt of Neutral (TSTglc − TSTneu)							
Frontal operculum	Right	54	0	18	3.2	p < 0.001	Y
Orbitofrontal cortex[a]	Right	42	46	−16	3.95	p < 0.05c	−
Receipt of Glucose > Anticipation of Glucose (TSTglc − ANTglc) masked exclusively by (TSTneu − ANTneu)							
Orbitofrontal cortex	Right	28	56	−14	4.92	p < 0.05wb	Y
Receipt of Salt > Receipt of Neutral (TSTslt − TSTneu)							
Frontal operculum	Right	56	8	20	4.23	p < 0.001	Y
Orbitofrontal cortex	Right	28	60	−12	3.45	p < 0.001	−

[a] Revealed by contrast sensitive to the effects of habituation across sessions (see text).
c—corrected for small volume restricted to region of interest.
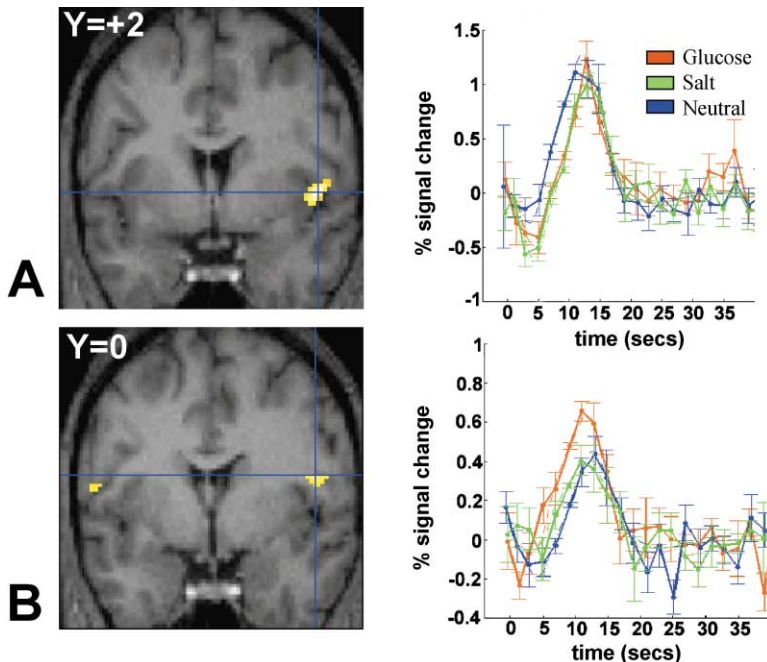wb—corrected for whole brain volume.

Figure 5. Responses in Insula/Frontal Operculum to Taste Receipt

(A) Area of right anterior insula/frontal operculum showing responses to all of the three taste stimuli as revealed by the conjunction of *TSTglc, TSTslt, and TSTneu* conditions (left) together with a time course of activation in this region produced by SPM99 from a single subject; and (B) area of frontal operculum showing greater activation to the receipt of pleasant taste than to the receipt of neutral taste as revealed by the *TSTglc − TSTneu* contrast (left) along with a corresponding time course from the same single subject (right).The threshold is set at p < 0.001 uncorrected for illustration.

al., 2000; O'Doherty et al., 2001a; Critchley et al., 2001; Breiter et al., 2001), rather than the simple paradigm used in this study (though see Knutson et al., 2000). Nevertheless, responses in the OFC and striatum have also been reported in these previous studies. However, few of these studies have observed responses in VTA/ Snigra (apart from Breiter et al., 2001) or amygdala. Further investigation is necessary to clarify whether a subset of these brain regions are preferentially involved in responding to natural rather than abstract rewards. Responses have previously been reported in the VTA and amygdala during the craving for or following infusion of drugs of abuse which may act directly on the midbrain dopamine system (Breiter et al., 1997; Sell et al., 1999). Consistent with data from animals (Wyvell and Berridge, 2000), our findings suggest that in humans, predictors of taste rewards may also act directly on this system.

Many of the areas found to respond during taste anticipation were shown to respond significantly more to the anticipation of the pleasant glucose taste than to the anticipation of the moderately unpleasant salt taste. This finding is important as there is currently a controversy about the extent to which the dopamine system is involved in responding to aversive as well as rewarding stimuli (Horvitz, 2000; Mirenowicz and Schultz, 1996; Spanagel and Weiss, 1999; Wilkinson et al., 1998). In the present study, voxels in the midbrain and striatum showed significantly greater responses to the anticipation of the pleasant glucose relative to the anticipation of the unpleasant salt stimulus, and the responses were not evident during the anticipation of the unpleasant stimulus in these regions when compared to the anticipation of the neutral taste. These findings suggest that in the human brain, these regions may be preferentially active during reward processing and not during the processing of aversive stimuli (at least over the time course measured). This finding accords with previous neuroim-

aging studies of aversive conditioning in which responses were not observed in the VTA/SNigra or striatum during the learning of associations between visual stimuli and aversive primary reinforcers such as loud noise (Büchel et al., 1998; LaBar et al., 1998), pain (Ploghaus et al., 1999), or aversive eye puffs (Ramnani et al., 2000).

Consistent with previous findings, we observed responses in OFC to the receipt of the salt taste, indicating that an unpleasant taste can activate this region (Zald et al., 1998; O'Doherty et al., 2001b). No responses were observed in the amygdala either to the anticipation or receipt of the salt taste. A lack of activation in the amygdala to the anticipation of salt taste is compatible with imaging studies of aversive conditioning, in which responses were observed in the amygdala during the early stages of learning that habituated rapidly (Büchel et al., 1998; LaBar et al., 1998). Given that in the present study, subjects were exposed to the contingencies prior to scanning, the amygdala response may have already habituated prior to the onset of the imaging experiment. The fact that the anticipatory amygdala response to the pleasant taste persisted throughout the experiment highlights a possible difference in the temporal profile of responses to pleasant and aversive stimuli, but clearly further investigation is necessary before drawing any firm conclusions on this issue. Another possible explanation for the lack of activation in amygdala as well as in striatal and midbrain regions to the salt taste is that the taste may not have been sufficiently aversive to recruit these regions. In future studies, it may be important to calibrate the concentration of the saline individually for each subject so that a strong aversive response is elicited in each subject. It is possible that differences observed between the anticipation of the glucose and salt tastes relate to intrinsic sensory differences between the two tastes rather than being due to differences

in affective aspects alone. However, we think that this alternative possibility is unlikely given that the main differences in anticipatory responses were in regions known to be involved in affective processing.

In conclusion, we have shown that in the human brain, expectation of a primary taste reward produces activation in areas with a high density of dopamine neurons or dopamine terminals, namely the VTA and striatum. These regions responded preferentially to reward and not to the anticipation of a moderately unpleasant taste. Furthermore, the finding of expectation-related responses in the amygdala and orbitofrontal cortex is consistent with animal lesion and neurophysiology studies and suggests that in the human brain, these areas play a role in reward expectation once stimulus-reward contingencies have been learned.

Experimental Procedures

Subjects
Eight healthy normal volunteers participated in the study (five Males, three Females; Mean age: 24.5; range 18–35). An additional four subjects were scanned but were excluded from the subsequent analysis due to technical problems with the scanning sequence or taste apparatus during the experiment. The data from a further subject were excluded due to strong discomfort reported during the scanning session. All subjects participated with full informed consent and the study was approved by the local research ethics committee.

Experimental Paradigm
In the task, one of three arbitrary visual stimuli were presented at the beginning of each trial, each associated with the subsequent delivery of either a pleasant sweet taste (1 M Glucose), an aversive salty taste (0.2M NaCl except in two subjects in which 0.1M NaCl was used; see Image Analysis), or an affectively neutral control solution (consisting of some of the main ionic components of saliva [25 mM KCl and 2.5 mM NaHCO$_3$]). After the presentation of the visual stimulus but prior to the delivery of the taste, there was a variable delay period ranging from 4 to 11 s (mean: 7.5 s). On each trial, 0.5 ml of the relevant taste solution was delivered to the subjects' mouth. The subjects were instructed to roll each taste about their tongue and then to swallow once they observed a visual cue which occurred 9.5 s after the initial delivery of the taste. A further delay of 3 s occurred, and at the beginning of the next volume acquisition (as triggered by a scanner pulse), the subsequent trial began. On each trial, the visual stimulus remained on the screen until after the taste was swallowed, when it was removed 3 s before the occurrence of the next trial. Each trial type occurred approximately 28 times throughout the experiment and in pseudorandom order. The specific stimulus-taste associations were also systematically varied across subjects. Once subjects had been placed in the scanner but prior to scanning, they received training with six presentations of each trial type. This was carried out to ensure that subjects had learned the stimulus-reinforcer contingencies prior to scanning, as the aim of the current experiment was to investigate the responses during reward anticipation once the contingencies had been well learned and not to investigate the responses occurring during learning per se. Following training, each subject was able to identify which stimulus was associated with which taste. Subjects were also instructed to minimize head movement during scanning, especially during swallowing, and subsequent analysis of subject motion did not reveal excessive scan to scan motion (of more than 1.5 mm in any direction). After scanning, subjects were asked to provide subjective pleasantness and intensity ratings for the three tastes (using a scale ranging from +2 = very pleasant, 0 = neutral, through to −2 = very unpleasant and similarly for intensity).

Apparatus
The tastes were contained in three 50 ml syringes which were attached to an SP220I electronic syringe pump (World Precision Instruments Ltd, Stevenage, UK), positioned in the scanner control room, and delivered to the subjects via three separate 6 m long 3 mm wide polythene tubes. The syringes were also attached to a computer controlled valve system which enabled the different tastes to be delivered independently along the tubing. The apparatus was controlled by a stimulus presentation program operating on a PC positioned in the control room, which also received volume trigger pulses from the scanner, and the visual stimuli were presented on a projector screen positioned ∼10 cm away from the subject's face.

Imaging Procedure
The functional imaging was conducted by using a 2 Tesla Siemens Vision MRI scanner to acquire gradient echo T2*-weighted echo-planar images (EPI) using a special sequence designed to minimize signal loss due to susceptibility gradients (Deichmann et al., 2002). One of the most frequently used techniques for this purpose, dubbed z-shimming (Frahm et al., 1988; Ordidge et al., 1994; Constable and Spencer, 1999; Glover, 1999), is based on the acquisition of a series of images with different preparation gradient pulses in slice selection direction. This compensates for spin dephasing due to through-plane susceptibility gradients. However, it has been shown that in the presence of local in-plane susceptibility gradients, a gradient echo data set represents a superposition of echo groups with different displacements in k space (Posse, 1992). This may reduce the local echo time in EPI sequences and thus the BOLD sensitivity. The compensation technique used in the present work includes preparation gradient pulses in phase encoding direction and in slice selection direction to correct simultaneously for echo time shifts and spin dephasing. Imaging was performed as follows: for each standard EPI volume acquisition (acquired with a TE = 35 ms), two additional volumes were acquired with preparation gradient pulses directly before image acquisition. The gradient pulses had a duration of 1 ms and the following amplitudes: image 1: phase direction = 4.5 mT/m, slice direction = −3.6 mT/m; image 2: phase direction = −2.5 mT/m, slice direction = −3.6 mT/m. A combined image was then calculated from the sum of squares (SSQ) of the correction volumes and the standard EPI volume in order to produce an image with maximum BOLD intensity in each voxel (see Figure 1B). It has been shown that the SSQ approach yields the highest t values (Constable and Spencer, 1999). Sixteen axial slices were acquired for each combined volume, with a slice thickness of 2 mm and a distance between slices of 1.5 mm. The slices were selected to enable coverage of the amygdala, orbitofrontal cortex, and midbrain dopaminergic nuclei ventrally, extending to the dorsal extent of the frontal operculum (see Figure 1C). The in-plane voxel size was 3 mm isotropic. The total acquisition time for each combined volume was 4.1 s. Due to the complexity of the sequence and limitations of scanner hardware, it was possible to acquire only 120 consecutive volumes in a single imaging run, and so for each subject, the experiment was conducted in four separate imaging runs of 8 min 12 s each (except in one subject where only three useable sessions were acquired). In addition, a T1-weighted structural volume (with 1 mm^3 voxel size) was acquired for each subject (Deichmann et al., 2000).

Image Analysis
The images were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). In order to correct for subject motion, the images were realigned to the first volume (Friston et al., 1995). The images were then spatially normalized to a standard T2* template with a resampled voxel size of 2 mm^3 (Friston et al., 1995), and spatial smoothing was applied using a Gaussian kernel with a full width at half maximum (FWHM) of 10 mm. Intensity normalization, high pass temporal filtering (using a filter width of twice the minimum intertrial interval), and low pass temporal filtering (using a Gaussian filter with FWHM of 4 s) were also applied to the data.

Following preprocessing of the data, statistical analysis was carried out by applying a fixed effects analysis using the general linear model across the eight subjects, in which each trial type was modeled as two separate conditions: taste anticipation and taste receipt. There were thus six effects of interest: anticipation of glucose, anticipation of salt, anticipation of neutral, glucose taste, salt taste, and neutral taste. The taste anticipation conditions were modeled as a variable length box-car regressor (with a variable epoch length of

4 to 11 s), and the taste receipt conditions were modeled as a fixed length box-car (of length 9.5 s). Each regressor was convolved with the canonical hemodynamic response function, and in order to account for small changes in the temporal onset of the events due to the use of the combined scanning sequence, the temporal derivative of each regressor was also included in the model. Residual motion effects were corrected for by including the six estimated motion parameters for each subject as regressors in the model. Additional effects of swallowing were incorporated by including a separate regressor to model the variance introduced by swallowing on each scan in which swallowing was cued to occur, as well as modeling swallowing as a distinct neural event with a corresponding hemodynamic response function. The regressors for the taste anticipation events and the corresponding taste receipt events were not completely orthogonal, but were sufficiently uncorrelated to permit differential effects to be detected.

T tests were carried out on linear contrasts of the regressors in order to produce statistical maps that identified voxels showing effects of reward anticipation and reward receipt relative to the other conditions. In the case of contrasts involving the salt anticipation or salt receipt conditions, the results from the two subjects who received 0.1 M NaCl instead of 0.2 M NaCl were excluded from the reported analysis (i.e., the analysis was restricted to six subjects for those contrasts; though in fact, the inclusion of these two subjects did not make any substantive difference to the overall result for those contrasts). In order to test whether activation in the orbitofrontal cortex and other regions had habituated over the course of the four separate imaging runs that constituted the experiment, contrasts were performed between the conditions restricted to the first two sessions only, masked by the direct comparison between the 1st and 4th sessions of the contrast in question (i.e., ANTglc or TSTglc). The aim of these contrasts was thus to detect areas that showed significant activation in the first half of the experiment that had habituated by the end of the experiment. This technique was used because each session was modeled separately and therefore it was not possible to test for habituation by fitting a regressor that incorporates a linear or exponential decay function over the whole experiment (e.g., as used by Büchel et al., 1998).

Anatomical localization was carried out with reference to the atlases of Duvernoy (1995, 1999), and with respect to the subjects' spatially normalized structural scans. The statistical threshold used to report activations was set at $p < 0.001$ uncorrected for regions of interest that were specified a priori. The regions in which responses to reward are predicted a priori are the midbrain (in particular the VTA), striatum, amygdala, and OFC. Furthermore, sensory responses in primary taste cortex (frontal operculum/insula) were also predicted to occur in response to the receipt of taste (see Rolls, 1997; O'Doherty et al., 2001b). A correction for multiple comparisons was performed within each region of interest using the theory of Gaussian Random Fields (Friston et al., 1994), and those activations which survived correction at $p < 0.05$ are indicated. Voxels within a region of interest were selected using a binary mask drawn over the anatomically defined boundaries of the region as delineated by the atlases of Duvernoy (1995, 1999) (apart from the VTA/SNigra in which a sphere of radius 10 mm positioned in the center of the VTA was used).

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