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# Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study

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**Abstract**

Findings from animal as well as human neuroimaging studies suggest that reward delivery is associated with the activation of subcortical limbic and prefrontal brain regions, including the thalamus, the striatum, the anterior cingulate and the prefrontal cortex. The aim of the present study was to explore if these reward-sensitive regions are also activated during the anticipation of reinforcers that vary with regard to their motivational value. A differential conditioning paradigm was performed, with the presentation of a rewarded reaction time task serving as the unconditioned stimulus (US). Depending on their reaction time, subjects were given (or not given) a monetary reward, or were presented with a verbal feedback consisting of being fast or slow. In a third control condition no task needed to be executed. Each of the three conditions was introduced by a different visual cue (CS). Brain activation of 27 subjects was recorded using event-related functional magnetic resonance imaging. The results showed significant activation of the substantia nigra, thalamic, striatal, and orbitofrontal brain regions as well as of the insula and the anterior cingulate during the presentation of a CS signalling a rewarded task. The anticipation of a monetary reward produced stronger activation in these regions than the anticipation of positive verbal feedback. The results are interpreted as reflecting the motivation-dependent reactivity of the brain reward system with highly motivating stimuli (monetary reward) leading to a stronger activation than those less motivating ones (verbal reward).


## Introduction

Brain regions that are responsive to reward delivery have been studied intensely over recent years. Findings from animal studies point to the important role of the striatum, the orbitofrontal cortex (Rolls, 1999; Schultz et al., 2000), the thalamus (Oyoshi et al., 1996; Komura et al., 2001), and the anterior cingulate (Bussey et al., 1997; Parkinson et al., 2000) for the processing of reward stimuli.

In humans comparable structures have been identified by using modern neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Here, the application of primary reinforcers (e.g., pleasant taste, touch, or smell) led to an activation of the orbitofrontal and prefrontal cortex, the insula, the anterior cingulate as well as the striatum (Francis et al., 1999; O'Doherty et al., 2002). The presentation of secondary reinforcers provoked similar activation patterns. In a study by Thut et al. (1997), the prefrontal, midbrain, and thalamic activation increased when correct responses in a go/nogo task were rewarded with money compared to verbal reinforcement. Delgado et al. (2000) used a gambling task, where subjects could win or lose money. Both conditions provoked activation in the bilateral caudate and the left ventral striatum. In another type of gambling task, Elliott et al. (2000) observed activation of the ventral striatum during reward presentation. Further, they were able to differentiate between those regions responding to a financial reward in general and those responding to high rewards occurring in

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the context of an increasing reward. Whereas the ventral striatum and subthalamic midbrain areas were sensitive to a general reward, the globus pallidus, the thalamus, and cingulate regions responded to the increasing rewards. Knutson et al. (2000) applied a reaction time task where the subjects could win or lose money depending on their task performance. In a control condition the performance had no consequence. During both reward and punishment, a significant activation of striatal (caudate and putamen) and thalamic regions as well as parts of the insula was found.

While these investigations focused on the effects of reward delivery, there also have been experiments on reward anticipation. This first phase of the reward processing is strongly linked with the concept of incentive motivation (Bolles, 1972). As could be demonstrated in animal studies, the most important brain structures involved in the anticipation of reward are dopaminergic and include midbrain regions (substantia nigra, ventral tegmental area) projecting to the striatum (nucleus caudatus, putamen, ventral striatum, in particular the nucleus accumbens) and the frontal cortex (Schultz, 1998; Ikemoto and Panksepp, 1999).

Recently, fMRI studies with human subjects could substantiate the importance of the aforementioned brain areas and the nucleus accumbens in particular for the anticipation of a reward. O'Doherty et al. (2002) used a cue paradigm with a visual stimulus as the cue and a taste stimulus as the reward. When analysing the anticipatory phase between cue and reward delivery they found activation in the ventral tegmental area, the substantia nigra, and the striatum including the nucleus accumbens. Knutson et al. (2001) investigated the anticipation of a monetary reward with a so-called monetary incentive delay task. In an event-related fMRI design, the authors revealed an increase of nucleus accumbens activation during reward but not during punishment anticipation. Furthermore, this activation was correlated with both the amount of monetary reward and the reported subjective happiness of the subjects. In contrast, medial caudate regions were involved during reward as well as punishment anticipation.

In both of the described fMRI studies on reward anticipation, the interval between the cue and the reward delivery was variable. Therefore, the subjects were not able to exactly foresee the reward onset. This type of unpredictability is suggested to be a necessary condition for the activation of the brain reward system (Schultz et al., 1997; Hollerman and Schultz, 1998; Mirenowicz and Schultz, 1994).

Within the present investigation we attempted to fulfil the unpredictability criterion in a different manner. The temporal uncertainty with regard to the reward delivery was removed from our design, which consisted of a differential conditioning paradigm with a fixed cue-reward interval. Instead, we varied the reinforcer value by introducing response-dependent reward intensities. The subjects had to execute a reaction time task serving as the unconditioned stimulus (US). Depending upon their performance, the subjects could either win (or not win) money in the first condition. In a second condition, they were presented with a verbal feedback consisting of being fast or slow, whereas in a third control condition no task had to be executed at all. Each of the three conditions was introduced by a different visual cue (CS).

In accordance with the relevant literature mentioned before (Knutson et al., 2001; O'Doherty et al., 2002), we predicted an activation of the reward system (the striatum, the ventral tegmental area, the substantia nigra, and in particular the nucleus accumbens) and additional reward-sensitive brain areas (the thalamus, the insula, and the orbitofrontal cortex) during the presentation of a CS that announces a rewarded reaction time task, compared to a CS announcing no task. Further, the anticipation of being able to obtain a monetary reward should be more motivating than the anticipation of a simple verbal feedback and therefore produce stronger activation in these regions.

## Materials and methods

### *Subjects*

Twenty-seven right-handed subjects (24 females, mean age M = 23.3 years) were recruited from the current psychology undergraduates at the University of Giessen. The large number of female subjects reflects the high percentage of women in our undergraduate population. All subjects received course credit and were paid 10 €. In addition, the subjects could increase this amount by gaining additional money during the course of the experiment. All subjects gave their informed consent prior to participating in the study.

### *Data acquisition*

Functional imaging data were acquired by a 1.5-T Siemens Symphony whole body MRI-scanner with a Quantum gradient system (Siemens, Erlangen, Germany). To measure the blood oxygenation level dependent (BOLD) contrast, a T2*-weighted single shot gradient echo EPI sequence (TA = 100 ms, TE = 60 ms, flip angle = 30°, FOV = 192 mm, 64 × 64 matrix) was used. One volume contained 20 slices with a 5-mm slice thickness (no gap) and covered all the brain regions of interest. The slices were acquired interleaved in ascending order. Between each volume, a 1-s interval had to be added, leading to a volume repetition time of 3 s. Prior to the functional measurement, a T1-weighted anatomical MRI scan was acquired for each subject.

### *Experimental design*

Before scanning, the subjects were instructed about the meaning of the different stimulus types used in the experiment. They were asked to respond to a bright flash of light as fast as they could by pressing a button mounted on a grip,

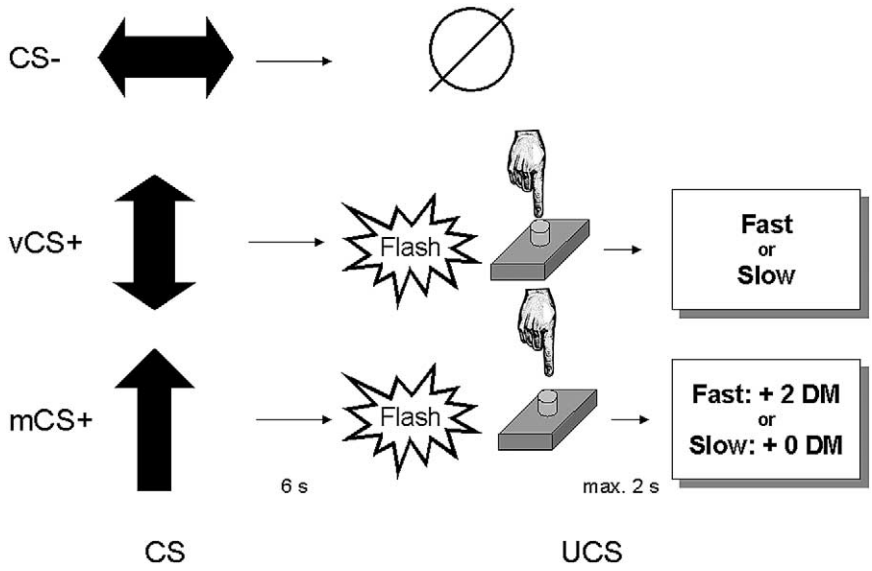



Fig. 1. The three experimental conditions used in the experiment. Subjects were instructed to respond to a flash that was presented following the presentation of the CS+ using a response button. CS presentation was 6 s for all conditions.

which they held in their right hand. During scanning, the subjects underwent three different types of trials (Fig. 1). The first CS, the monetary reward CS+ (mCS+), was a vertically oriented arrow pointing upward. It was presented for 6 s and immediately followed by the US task. After the button press, a verbal feedback ("fast" or "slow") together with the information about the earned amount (either 2 German marks = approx. 1 € or 0 €) was given. The threshold for a fast response was adaptive for each subject and each trial to ensure that all subjects were able to win some money and work on their maximum performance level. The adaptive algorithm was a simple increase of 5% of the threshold after a slow response and a 10% decrease after a fast response.

The second CS+, the verbal reward CS+ (vCS+), consisted of a vertically oriented double-sided arrow. The only difference to the mCS+ was that the feedback contained no information about a monetary gain. The CS− was a horizontally oriented double-sided arrow. The CS− was followed by a black screen for 3 s to include a control condition without any anticipation of a consequence. Two seconds after each CS+ trial, the actual account balance was displayed for 2 s. The intertrial interval was randomly varied between 6 and 9 s. Each condition was presented 20 times in a pseudo-randomized trial order with no more than two equal conditions in succession.

The stimuli were presented with an LCD projector on a screen on the backside of the scanner. The subjects were able to watch the screen, using a mirror located approximately 20 cm above their eyes.

*Data analysis*

The fMRI data were analysed using statistical parametric mapping methods (Friston et al., 1995; Friston, 1996) with the SPM99 software package (The Wellcome Department of Cognitive Neurology, London, England). During preprocessing, the EPI images were corrected for sequential slice timing. In a subsequent step all images were realigned to the first image to adjust for possible head movements. The realigned images were then spatially normalized to a standard EPI template (Ashburner and Friston, 1999) to allow averaging across subjects. In the last preprocessing step, all functional images were smoothed by using a 6-mm (full width at half maximum) isotropic Gaussian kernel.

The evoked BOLD responses were modelled for the three CS conditions as well as the task conditions (task with reward, task without reward, no task). A synthetic hemodynamic response function was used for response modelling. To account for movement related variance that might be correlated to the experimental design, the 6 movement parameters (3 translations, 3 rotations) that were derived from the realignment preprocessing step were included as covariates into the analysis.

To test differences between conditions, linear contrasts were applied to the estimates of the parameters for each condition. The data were first analysed separately for each subject. Due to the relatively high number of subjects ($n$ = 27), the contrast images of each subject were then included into a random-effects second level analysis. The resulting $P$ values of the $t$ statistic for the specific contrasts were adjusted for multiple comparisons within the entire volume using the Gaussian random field theory (Worsley et al., 1996). Although we did not apply region of interest analyses to our data, all fMRI analyses focused on reward system-related target regions that were described in the introduction. These are the thalamus, the striatum, the substantia nigra, the orbitofrontal cortex, the cingulate gyrus, and the

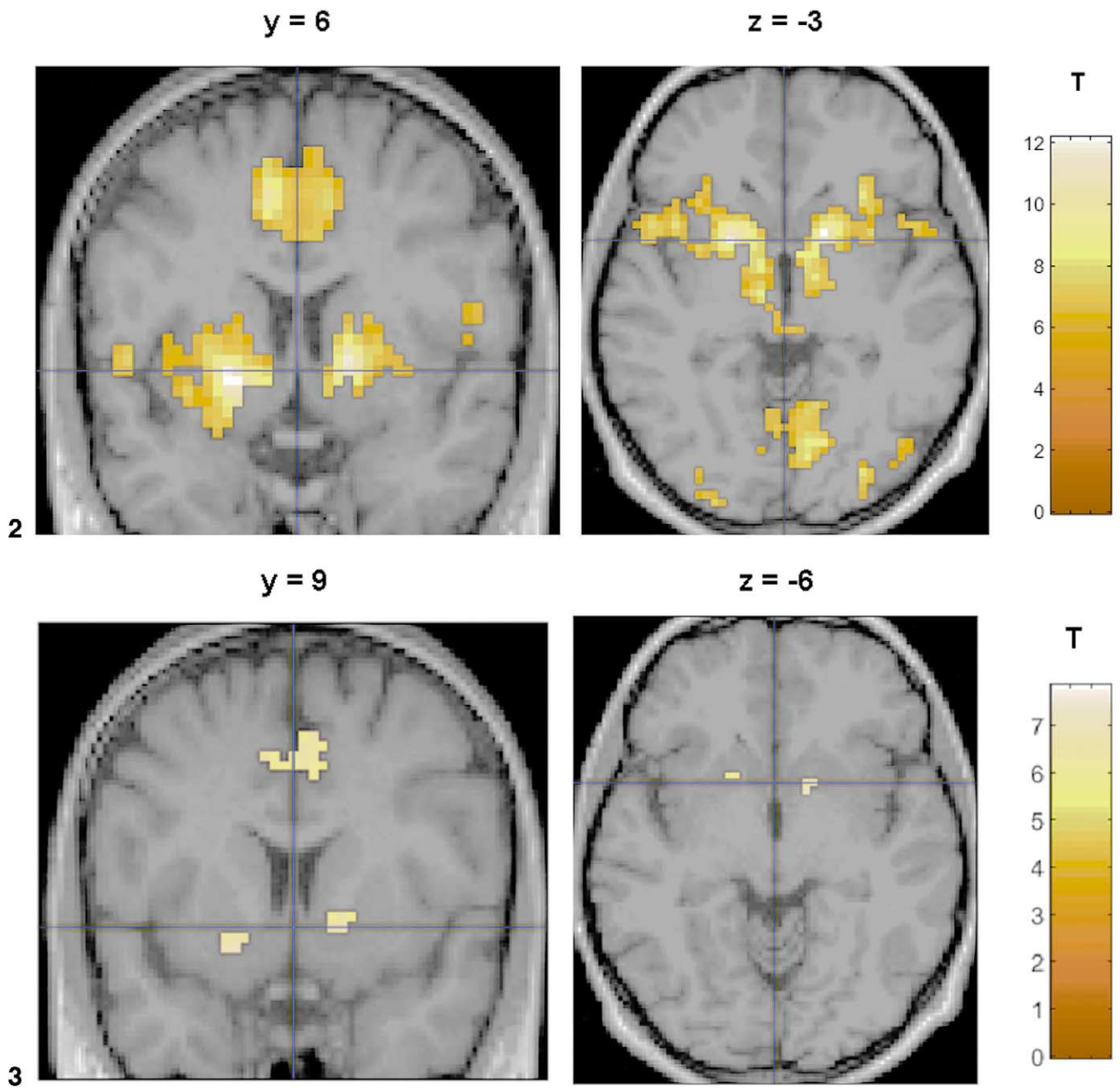


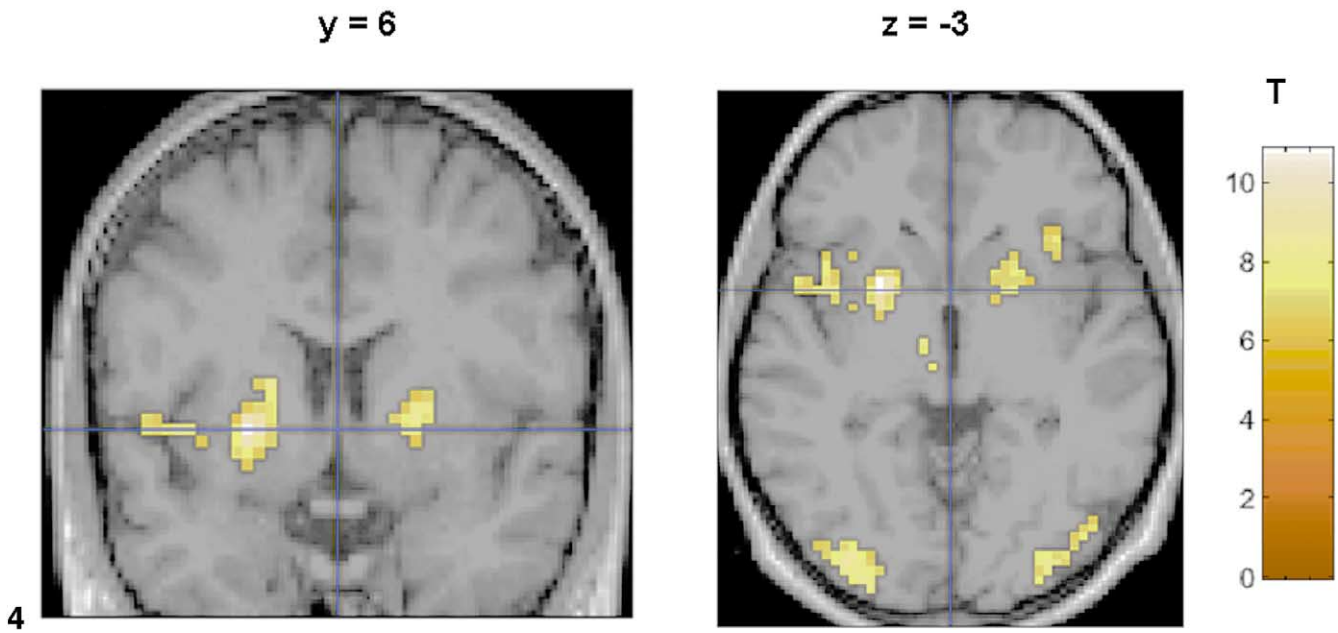

Fig. 2. Significant striatal, cingulate gyrus, insula, and prefrontal activations as revealed by the contrast mCS+ > CS− exemplarily displayed for a transversal and a coronal slice ($P < 0.05$, corrected).
Fig. 3. Significant striatal (nucleus accumbens, putamen) and cingulate gyrus activations as revealed by the mCS+ > vCS+ contrast, exemplarily displayed for a transversal and a coronal slice ($P < 0.05$, corrected).

insula. Significant activations outside these regions are reported as well.

## Results

All subjects participating in the experiment won money, on average € 10.89 (range € 3.00–13.30, SD 2.15). The number of task omissions was rather small, indicating a sufficient task involvement. The mean omission rates of the two reaction time conditions were comparable (mCS+: M = 0.29, vCS+: M = 0.37) which had been tested with a paired *t* test; 17 subjects had none, 6 subjects had one, 2 subjects two, and 2 more subjects four omissions.

Since we had predicted that the motivational variation of the reinforcers would influence the task performance, we compared the median of the reaction times toward the US between the mCS+ and the vCS+ condition by using a



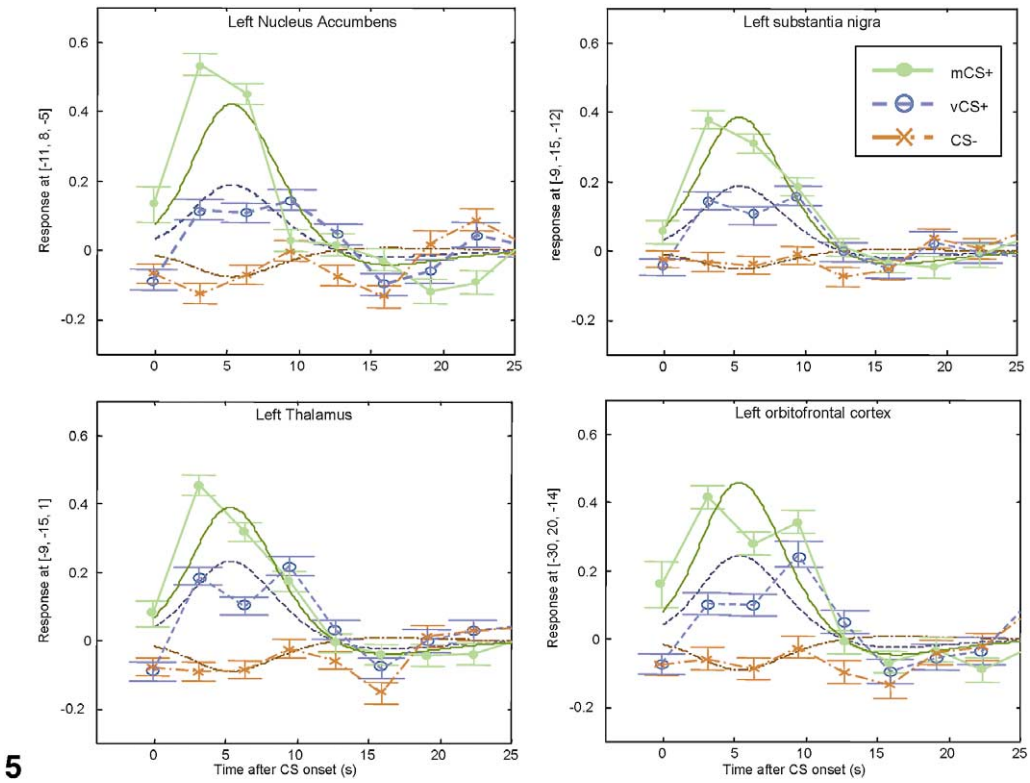




Fig. 4. Significant striatal (putamen), right orbitofrontal, left insula, and bilateral occipital activations as revealed by the vCS+ > CS− contrast, exemplarily displayed for a transversal and a coronal slice ($P < 0.05$, corrected).

Fig. 5. Fitted responses and peristimulus time histograms for the three experimental conditions in four regions of interest as revealed by an explorative fixed effects analysis ($N = 27$). The solid green lines represent the mCS+, the dashed blue lines the vCS+ and the dash-dot red lines the CS−. Voxel were selected using the most significant voxel in each region from the mCS+ > CS− contrast (compare Table 2).

pairwise *t* test. As expected, the responses to the mCS+ were significantly faster than to the vCS+ [mCS+: 249.0 ms; vCS+: 290.9 ms.; $t(26) = 4.73$, $P < 0.001$].

To identify brain regions activated during the presentation of a motivating CS+, we first compared the effects of the mCS+ with the CS− presentation. This contrast should reveal significant activation in those regions sensitive to the motivational aspect of the stimulus as well as to the association between CS and US. Significant activation was found in all target regions: the thalamus, the substatia nigra,

Table 1
Locations and *T* values for the significant activations for the contrast mCS+ > CS−[a]

| Area (Talairach label/Brodman's area) | $T_{Max}$ | Talairach coordinates | | |
|---|---|---|---|---|
| | | *x* | *y* | *z* |
| Left thalamus | 9.61 | −9 | −15 | 1 |
| Right thalamus | 9.36 | 18 | −8 | 9 |
| Left substantia nigra | 7.36 | −9 | −15 | −12 |
| Right substantia nigra | 8.50 | 9 | −24 | −9 |
| Left nucleus accumbens | 7.69 | −11 | 8 | −5 |
| Right nucleus accumbens | 9.18 | 13 | 8 | −4 |
| Left putamen | 12.14 | −21 | 6 | −5 |
| Right putamen | 11.95 | 15 | 9 | −3 |
| Left globus pallidus | 8.78 | −15 | −9 | −7 |
| Right globus pallidus | 8.32 | 18 | −12 | 1 |
| Left orbitofrontal cortex (BA 47) | 7.58 | −30 | 20 | −14 |
| Right orbitofrontal cortex (BA 47) | 7.61 | 27 | 14 | −16 |
| Left cingulate gyrus (BA 24) | 9.92 | −9 | 8 | 44 |
| Right cingulate gyrus (BA 32) | 9.77 | 6 | 16 | 35 |
| Left insula (BA 13) | 7.04 | −50 | −22 | 20 |
| Right insula (BA 13) | 9.69 | 36 | 20 | 2 |
| Left cuneus (BA 17) | 9.53 | 0 | 84 | 10 |
| Left lingual gyrus (BA 17) | 7.69 | −18 | −97 | −8 |
| Right lingual gyrus (BA 18) | 9.75 | 18 | −70 | −12 |
| Left middle occipital gyrus (BA 18) | 7.54 | −27 | −96 | 5 |
| Right middle occipital gyrus (BA 18) | 8.82 | 30 | −85 | −1 |
| Left inferior occipital gyrus (BA 18) | 7.67 | −36 | −82 | −6 |
| Left precentral gyrus (BA 4) | 7.93 | −39 | −15 | 57 |
| Right precentral gyrus (BA 6) | 7.24 | 48 | −1 | 41 |
| Left medial frontal gyrus (BA 6) | 6.82 | −9 | −21 | 45 |
| Right medial frontal gyrus (BA 6) | 7.52 | 50 | 5 | 47 |

[a] In the upper part of the table, the most significant voxels within the target regions are displayed. In the lower part, the most significant voxels of the significantly activated clusters outside these regions are displayed.

the striatum (nucleus accumbens, putamen, globus pallidus), the orbitofrontal cortex, the anterior cingulate, and the insula (Fig. 2). In Table 1, the most significant voxels from the activated clusters are displayed.

We further observed significant bilateral activation in the occipital lobe (BA 17, 18, and 19) as a result of the visual stimulation. In addition, as a consequence of the reaction time task, the left motor cortex (left BA 4 and 6, right BA 6) was involved.

To investigate whether the monetary reward activated the reward system more strongly than the verbal feedback, and also to eliminate the CS-US contingency effects, we compared the mCS+ with the vCS+ condition. For this contrast we found fewer activated regions. However, thalamic, striatal (bilateral putamen and right nucleus accumbens), and orbitofrontal regions again showed significant activation. However, the clear bilateral pattern did not occur in this contrast (Table 2). As can be seen in Fig. 3, the striatal activation that remained in this contrast was localized in the nucleus accumbens.

Finally, to test whether verbal feedback was also suitable to activate the motivational system in the brain we compared the vCS+ with the CS− condition (Fig. 4). The

Table 2
Locations and *T* values for the significant activations for the contrast mCS+ > vCS+[a]

| Area (Talairach label/Brodman's area) | $T_{Max}$ | Talairach coordinates | | |
|---|---|---|---|---|
| | | *x* | *y* | *z* |
| Left thalamus | 6.37 | 0 | −5 | 9 |
| Right thalamus (medial dorsal nucleus) | 7.46 | 6 | −14 | 6 |
| Left substantia nigra | 6.42 | −9 | −18 | −7 |
| Right nucleus accumbens | 6.82 | 12 | 8 | −6 |
| Left putamen | 7.08 | −18 | 8 | −11 |
| Right putamen | 6.50 | 16 | 8 | −3 |
| Left orbitofrontal cortex (BA 47) | 6.87 | −24 | 17 | −11 |
| Left cingulate gyrus (BA 24) | 7.07 | −3 | 2 | 39 |
| Right cingulate gyrus (BA 24) | 7.83 | 3 | −4 | 39 |
| Right insula (BA 13) | 7.25 | 33 | 20 | 2 |
| Right lingual gyrus (BA 19) | 6.22 | 15 | −62 | −17 |
| Right precentral gyrus (BA 6) | 6.41 | 50 | 2 | 44 |

[a] In the upper part of the table, the most significant voxels within the different target regions are displayed. In the lower part, the most significant voxels of the significantly activated clusters outside these regions are displayed.

degree of significantly activated target regions was reduced compared to the mCS+ vs. CS− contrast. We still were able to detect activation in the thalamus, the striatum (bilateral putamen and right globus pallidus), the orbitofrontal cortex, the right anterior cingulate, and the left insula (Table 3).

Besides the activation of the target regions, significant

Table 3
Locations and *T* values for the significant activations for the contrast vCS+ > CS−[a]

| Area (Talairach label/Brodman's area) | $T_{Max}$ | Talairach coordinates | | |
|---|---|---|---|---|
| | | *x* | *y* | *z* |
| Left thalamus | 7.90 | −9 | −12 | −2 |
| Right thalamus | 7.02 | 6 | −3 | 0 |
| Left putamen | 10.82 | −24 | 6 | −3 |
| Right putamen | 8.30 | 21 | 6 | 0 |
| Right globus pallidus | 6.65 | 15 | 5 | 0 |
| Left orbitofrontal cortex (BA 47) | 7.10 | −42 | 17 | −8 |
| Right orbitofrontal cortex (BA 47) | 8.26 | 36 | 20 | −1 |
| Right anterior cingulate (BA 32) | 7.40 | 9 | 25 | 26 |
| Left insula (BA 13) | 8.10 | −42 | 12 | −1 |
| Left cuneus (BA 17) | 8.33 | 0 | −84 | 10 |
| Right cuneus (BA 18) | 7.25 | 6 | −83 | 24 |
| Right inferior occipital gyrus (BA 18) | 10.04 | 39 | −85 | −6 |
| Left middle occipital gyrus (BA 18) | 9.25 | −36 | −87 | −1 |
| Right middle occipital gyrus (BA 18) | 8.72 | 45 | −76 | −9 |
| Right lingual gyrus (BA 18) | 7.72 | 18 | −68 | 12 |
| Left inferior occipital gyrus (BA 18) | 9.55 | −36 | −32 | −6 |
| Right inferior occipital gyrus (BA 18) | 8.45 | 30 | −90 | −3 |
| Right fusiform gyrus (BA 19) | 6.53 | 24 | −62 | −10 |

[a] In the upper part of the table, the most significant voxels within the different target regions are displayed. In the lower part, the most significant voxels of the significantly activated clusters outside these regions are displayed.

bilateral occipital activation (BA 17, 18, and 19) occurred. Interestingly, deviating from the mCS+ vs. CS− contrast, no motor areas were involved.

The results reported before indicate a positive relationship between the intensity of the anticipated reward and the degree of activation in the target regions, reaching from no activation during the CS− condition to the largest activation in the mCS+ condition. To substantiate this interpretation derived from a visual inspection of the data, we did a post hoc analysis of our data. We looked at the average hemodynamic responses of all subjects in the nucleus accumbens, the thalamus, the substantia nigra, and the orbitofrontal cortex. We calculated a first level fixed effects model for all subjects and looked at the fitted responses as derived from the SPM analysis for the three CS− conditions. In Fig. 5 we plotted the fitted responses from those voxels that showed the most significant activation in the mCS+ > CS− contrast together with the peristimulus time histograms. According to Fig. 5, in all these regions, there is a clear pattern with the greatest responses to the mCS+, medium responses to the vCS+, and the smallest responses (or even a signal reduction) to the CS−. Thus, increased activation went along with an increasing motivational value.

To confirm this impression, a mixed model conjunction analysis was performed as recommended by one reviewer. On the first level, the conjunction analysis was conducted using the vCS+ > CS− and the mCS+ > vCS+ contrasts. The resulting contrast images of all subjects were included into a random effects analysis, which should identify those regions that show an increasing response towards increasing motivation (CS− < vCS+ < mCS+). Since the conditions of our experiment were not orthogonal, SPM performed an orthogonalization before calculating the conjunction analysis. For this orthogonalization, the contrasts were included in the same order (from CS− < vCS+ to vCS+ < mCS+). The results of this analysis was in line with the visual inspection of the peristimulus plots. In all the regions presented in Fig. 5, and most of our target regions, a significant activation showed up when using the same stringent significance threshold of $P < 0.05$ corrected for the entire volume (Table 4 and Fig. 6).

Finally, we did a post hoc analysis of the behavioral data, since it could be argued that differences between the two CS+ conditions are a result of differences in the task involvement. To estimate the behavioral variance in our experiment, we took a closer look at our performance data. Using a Mann-Whitney *U* test to compare the between-subject variance of the reaction times, we found that the between-subject variance was significantly smaller for the financially rewarded task than for the verbally rewarded task ($Z = -3.259$, $P < 0.001$, Fig. 7, left panel). Furthermore, the within-subject variance was also smaller for the financially rewarded task than for the verbally rewarded one (Wilcoxon test, $z = -1.54$, $P < 0.07$, one-sided, see Fig. 7, right panel).

Table 4
Locations and *T* values for the significant activations for conjunction analysis including the CS− > vCS+ and the vCS+ > mCS+ contrasts.[a]

| Area (Talairach label/Brodman's area) | $T_{Max}$ | Talairach coordinates | | |
|---|---|---|---|---|
| | | *x* | *y* | *z* |
| Right thalamus | 8.99 | 6 | −14 | 6 |
| Right substantia nigra | 7.56 | 9 | −21 | −14 |
| Left nucleus accumbens | 6.52 | −10 | 6 | −5 |
| Right nucleus accumbens | 7.40 | 12 | 9 | −6 |
| Left putamen | 6.42 | −27 | 6 | 2 |
| Right putamen | 9.14 | 15 | 6 | −3 |
| Left orbitofrontal cortex (BA 47) | 6.51 | −33 | 20 | −1 |
| Right orbitofrontal cortex (BA 47) | 6.71 | 53 | 20 | −11 |
| Left cingulate gyrus (BA 24) | 8.12 | −3 | 2 | 39 |
| Right cingulate gyrus (BA 32) | 8.02 | 6 | 16 | 35 |
| Right insula (BA 13) | 9.05 | 33 | 20 | 2 |
| Left fusiform gyrus (BA 19) | 7.37 | −33 | −79 | −16 |
| Right fusiform gyrus (BA 37) | 8.74 | 33 | −59 | −17 |
| Left lingual gyrus (BA 19) | 6.58 | −15 | −65 | −9 |
| Right lingual gyrus (BA 18) | 8.08 | 15 | −70 | −4 |
| Left precentral gyrus (BA 4) | 6.5 | −39 | −12 | 53 |
| Left medial frontal gyrus (BA 6) | 6.34 | −45 | −6 | 53 |

[a] In the upper part of the table, the most significant voxels within the different target regions are displayed. In the lower part, the most significant voxels of the significantly activated clusters outside these regions are displayed.

## Discussion

The present study investigated whether structures of the brain reward system can be activated during the anticipation of a reward and whether this activation varies with the motivational value of the reinforcer.

The results of the computed fixed effects model and the conjunction analysis showed that regions, which previously have been identified as responsive to reward delivery, are also involved in reward anticipation. The target regions (nucleus accumbens, putamen, globus pallidus, substantia nigra, thalamus, cingulate, and orbitofrontal cortex) were activated during the processing of both types of rewards, monetary and verbal. The identified structures correspond with the dopamine reward system as described by Schultz (1998). He proposed that when a reward-predicting conditioned stimulus is presented, dopamine is released by the substantia nigra and ventral tegmentum after having received impulses from striatal regions and the frontal cortex. Although we do not have a direct indicator of the dopamine release, and the changes in the BOLD signal mirror general neural activity (Logothetis et al., 2001), we do think that the simultaneous activation of aforementioned structures reflects the involvement of the dopaminergic reward system, with the nucleus accumbens being a key structure (Ikemoto and Panksepp, 1999; Knutson et al., 2001).

The computed second level random effects analysis indicated that the brain reward system is more strongly activated during the anticipation of the monetary reward com-

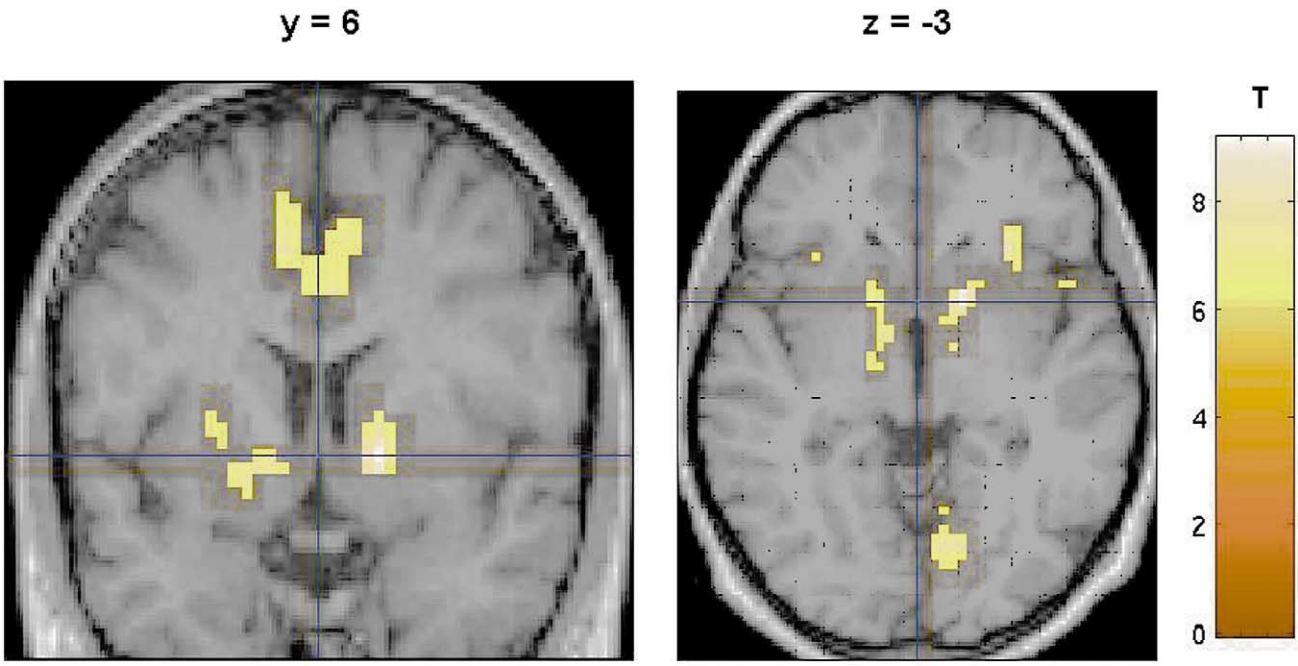



Fig. 6. Significant striatal (nucleus accumbens, putamen), orbitofrontal, right insula, bilateral cingulate gyrus, and right occipital activations as revealed by the conjunction analysis including the vCS+ > CSm and the mCS+ > vCS+ contrasts, exemplarily displayed for a transversal and a coronal slice ($P < 0.05$, corrected).

pared to the anticipation of positive verbal feedback. The nucleus accumbens and the substantia nigra, those regions that play a specific role in the reward system, were only found to be significantly activated when money could be won. We interpret these results as mirroring the motivation-dependent reactivity of the brain reward system, with highly motivating stimuli (monetary reward) leading to a stronger activation compared to less motivating ones (verbal reward). This interpretation is also in line with the behavioral data. The average reaction time of the subjects was significantly shorter in the monetary reward condition than in the verbal reward condition. Further, the performance was more consistent when the subjects expected a financial gratification. The within-subject as well as the between-subjects reaction time variance was smaller in the trials with monetary rewards compared to the trials with verbal rewards.

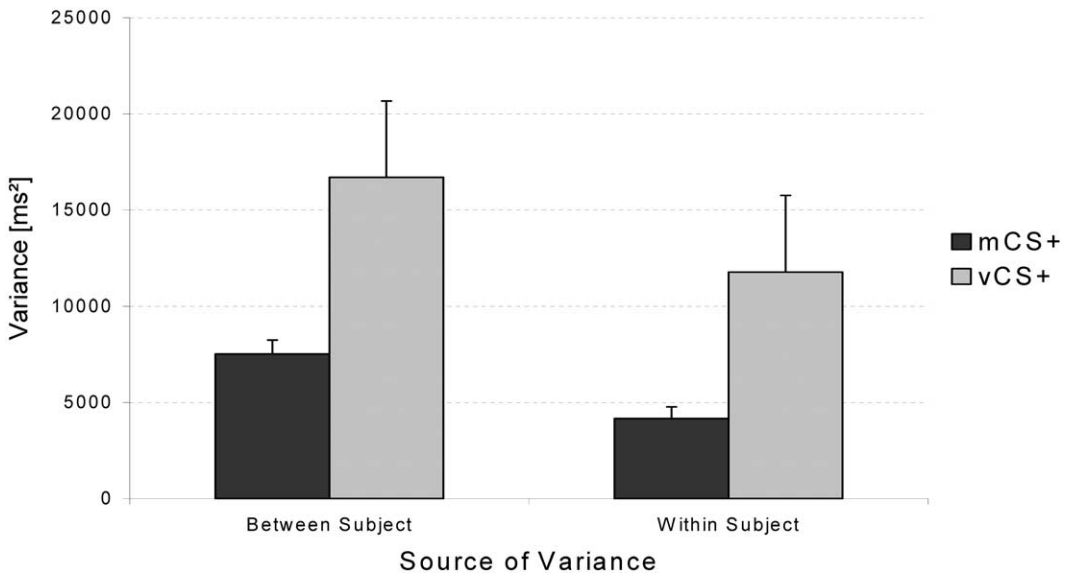



Fig. 7. Mean variance and SEM of the reaction times to the flash light for the two CS+ conditions. The left panel displays the variance between the subjects and the right panel displays the variance within the subjects.

A potential shortcoming of the present study was the control condition used for the differential conditioning paradigm. The CS− condition differed in several aspects from the CS+. Not only the US feedback, but also the flash and the motor response had to be removed from this condition to avoid any anticipatory processes. Therefore, the observed activation in the computed contrasts where the CS− condition was included could also be a consequence of the task differences rather than being related to the reward anticipation differences. However, the fact that the same regions could be identified in the contrasts including the CS− and those including the two CS+ conditions supports our conclusion that the activation mirrors reward anticipation. Furthermore, our analyses showed a linear activational increase in the reward-sensitive regions with increasing degrees of reward anticipation.

Another shortcoming of our study refers to our sample, which predominantly consisted of females. Thus, our conclusions are up until now restricted to this gender and need to be extended to males. This is currently being done in an ongoing project. First analyses indicate that the effects are not gender specific.

An asset of our investigation is the applied method. We could demonstrate that the unpredictability of the reinforcer, which triggers the activation of the brain reward system, does not necessarily have to be a temporal one as suggested by Schultz and colleagues (Schultz et al., 1997; Hollerman and Schultz, 1998; Mirenowicz and Schultz, 1994). Due to our adaptive performance threshold, we maximized the uncertainty for the subjects concerning the reward delivery without varying the CS-US interval. Therefore, it seems highly likely that our task continued to activate the reward system even after the CS-US contingency had been completely learned by the subjects, whereas in an instrumental learning paradigm, additional dopamine is not released after a task has been fully acquired (Ljungberg et al., 1992; Mirenowicz and Schultz, 1994).

In addition to the regions of the reward system we also studied some other structures that have been found to be reward-sensitive in previous studies. Elliott et al. (2000) reported activation of the insula during both reward and punishment conditions. In an fMRI study, Buechel et al. (1999) observed insula activation to the CS+ in a differential classical conditioning design. In contrast to the present study, the authors used an aversive US and interpreted their insula activation as reflecting the processing of the emotional content of the CS+. Since we could demonstrate before that the association of a CS+ with a rewarded task changed the emotional context of the CS+ itself (Volz and Kirsch, 2000), we believe that the insula involvement found in the present investigation also mirrors the emotional context of the conditioned stimuli. This interpretation is in accordance with an fMRI result from our own lab, identifying the insula as an emotion-sensitive area (Schienle et al., 2002).

A region with bilateral projections from the insula is the anterior cingulate gyrus (AC; BA 24; see Augustine, 1996). The AC has been described as an important region for the regulation of autonomic responses like skin conductance (Fredrikson et al., 1998; Zahn et al., 1999) and arterial blood pressure as an indicator of sympathetic activation (Critchley et al., 2000). Since this region was found to be activated in the present study, this could reflect autonomic arousal involvement. This interpretation follows the findings by Critchley et al. (2001) who used a financially rewarded task. The observed AC activation during the reward anticipation was modulated by the degree of anticipatory arousal as indexed by the skin conductance. A further role of the AC is visual attention (Woldorff et al., 1999). Carter et al. (1998) showed that this structure is involved in the regulation of behavior by monitoring the performance and detecting errors. Ochsner et al. (2001) suggest that the AC not only monitors the performance, but also decodes the motivational significance of stimuli. These interpretations of the AC function are in accordance with our detection of cingulate gyrus activation during task anticipation. Parkinson et al. (2000) performed a lesion study with rats and showed that the connection of the AC with the nucleus accumbens is important for the acquisition of Pavlovian approach behavior. Although the autoshaping procedure used in their paradigm is not comparable with our task, in both cases, a Pavlovian conditioning paradigm was used to induce motivated behavior. Even if we take into account that the coactivation of striatal and AC regions detected by fMRI is not a clear indicator for connections between these structures, our data fit in very well with those approaches postulating a link between ventral striatal and AC regions during the acquisition of motivated behavior.

In summary, we were able to demonstrate that the brain reward system is activated during reward anticipation and not only during its delivery. Obviously, already the expectancy of a positive outcome has a reward value, which motivates the individual to show the adequate behavior to increase the possibility to indeed receive the reinforcer.

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