Neural correlates of frustration

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Psychological considerations suggest that the omission of rewards in humans comprises *two* effects: first, an allocentric effect triggering learning and behavioural changes potentially processed by dopaminergic neurons according to the prediction error theory; second, an egocentric effect representing the individual's emotional reaction, commonly called frustration. We investigated this second effect in the context of omission of monetary reward with functional magnetic resonance imaging. As expected, the contrast omission relative to receipt of reward led to a *decrease* in ventral striatal activation consistent with prediction error theory. *Increased* activation for this contrast was found in areas previously related to emotional pain: the right anterior insula and the right ventral prefrontal cortex. We interpreted this as a neural correlate of the egocentric effect. *NeuroReport* 16:669–672 © 2005 Lippincott Williams & Wilkins.

Key words: Frustration; Functional magnetic resonance imaging; Hurt feelings; Omission of reward; Prediction error; Reward

INTRODUCTION

Attaining a desired objective is a satisfying experience for nearly everyone. But most people are at least as familiar with the feeling that accompanies experiences of not achieving a desired goal. This feeling is commonly referred to as frustration and characterizes the emotional reaction that follows the omission of a rewarding event or item.

Animal studies have helped to find brain areas and networks involved in *anticipating and attaining* rewards, such as the midbrain dopamine system and, especially, the ventral striatum [1]. These results have been reproduced by imaging research in humans using a wide variety of rewarding stimuli like food [2], drink [3], cultural objects [4] or money [5]. Investigations in nonhuman primates suggest that one of the most important functions of the dopaminergic reward system is the prediction of rewards and determination of whether predictions about outcomes are violated or verified. In this context, some evidence exists for a phasic decrease of dopaminergic activity owing to the omission of rewards [6], mainly interpreted as coding a prediction error or learning signal that is supposed to trigger learning and adaptation of future behaviour. The few studies of the human reward system dealing with omission of reward have replicated the role of dopaminergic brain areas [7,8] in coding the prediction error. But at any rate, in humans, the omission of rewards seems to have at least *two* effects [9]: First, an allocentric effect that makes the subject update his or her knowledge about the environment and which might be processed by dopaminergic neurons according to the prediction error theory. Second, an egocentric effect representing the individual's emotional reaction to the incident, commonly known as frustration. The neuronal bases of this second effect have not been investigated to date.

Hypotheses about the brain regions that might be involved in the emotional processing of frustration come from the investigation of social exclusion. In a functional magnetic resonance imaging (fMRI) study, Eisenberger *et al.* [10] recently studied the neuronal correlates of rejection in the social context of an interactive game and found regions that parallel studies of physical pain to be active. They concluded that emotional pain might have similar neural correlates as physical pain. This hypothesis is supported by a finding of Singer *et al.* [11] who found regions processing physical pain active during mere emotional empathy for pain. Social interaction is undoubtedly an important goal for humans with rewarding impact and has been shown to activate the reward system [12]. On the contrary, being excluded from or deprived of social interaction, despite efforts made to participate, certainly causes a feeling of frustration. But frustration does not occur only in social contexts. Therefore, we considered an involvement of the neural pain processing system, when dealing with hurt feelings or emotional pain, with the character of frustration in general. To test our hypothesis in an fMRI study, we chose a simple delayed incentive task with monetary reward. To build up frustrating circumstances, rewards were dispensed noncontingent to behaviour. Participants were informed that they had a chance to win money only if they responded correctly, but that a number of trials would not be rewarded despite correct responses. We expected to find neural correlates for both proposed mechanisms of processing omission of rewards: (1) changes in activity in dopamine-rich areas of the forebrain mediating signals for learning and adaptation to the environment and (2) activity within limbic brain areas processing the emotional reaction.

MATERIALS AND METHODS

Twelve healthy right-handed participants (six women; aged 21–33 years) with no history of psychiatric disease gave written informed consent. The study was approved by the local ethics committee of the University of Ulm. Before

scanning, all participants completed a practice version of the task. During scanning, participants performed two sessions (10 min each) of the task.

Task: We used a monetary incentive task with a parametric variation of possible wins (1 euro, 20 cents, no win). Each session consisted of 60 trials (6250 ms each; 10 no-win trials, 25 trials with potential gain of 1 euro and 25 trials with potential gain of 20 cents). Each trial started with one of three symbols (cue, 750 ms) indicating the possible amount of money to be won. After an expectation period (delay, 3000 ms), participants had to react correctly with a left (index finger, right hand) or right (middle finger, right hand) button press to two symbols (a square or a triangle; target) within a fixed interval of 1 s. Participants were notified in advance about the symbol/button press relationship (square/right, triangle/left or vice versa). In reacting correctly they provided themselves with a 60% chance of winning the announced amount of money (1 euro or 20 cents: win trial). In 40% of the trials, participants were not rewarded despite pressing the correct button (omission trial). Incorrect button presses resulted in a feedback of zero euros. Win and omission trials and the three trial types (1 euro, 20 cents, no win) appeared in random order. In the control trials, no money was announced; participants had only to press an arbitrary button (index or middle finger, right hand) and could not win any money. To make sure that all trials included a button press of some kind, participants were told that they would lose 1 euro if no button press occurred. Feedback (outcome, 1500 ms) followed the target's disappearance. Participants were notified about the amount of money they won in each trial with '1.00', '0.20' or '0.00' appearing on the screen. Reaction times and errors were registered.

Functional magnetic resonance image acquisition: A 1.5 T Siemens SYMPHONY Scanner (Siemens, Erlangen, Germany) equipped with a head coil was used to acquire T1 anatomical volume images ($1 \times 1 \times 1$ mm voxels) and fMRIs. Seventeen axial slices were acquired (64×64 pixels, FoV: 192 mm, slice thickness: 2.2 mm, 1.1 mm gap). Slices covered temporal and occipital lobes, inferior and lateral frontal lobes and subcortical structures including the basal ganglia but not the superior frontal and parietal lobes. A total of 401 volumes were obtained during each of the two sessions (TR 1500 ms, TE 40 ms, flip 90°) using a T2*-sensitive gradient echo sequence.

Functional magnetic resonance image analysis: fMRI data were analysed event-related using BrainVoyager 4.9 (Brain-Innovation, R. Göbel, Maastricht, The Netherlands), focussing on changes in blood-oxygenation-level-dependent contrast during expectation and feedback periods. Images were preprocessed including motion correction, slice scan time correction, high-frequency temporal filtering and removal of linear trends. Functional images and anatomical images were coregistered and transformed into Talairach space [13]. Spatial smoothing was applied with a kernel of 4 mm full-width-half-maximum.

Individual time series data were analysed using a general linear model for autocorrelated observations [14] with six orthogonal regressors of interest as described by Knutson *et al.* [5] and six regressors for residual motion. Regressors of interest contrasted: (con1) expectation period versus target and outcome period, (con2) expectation of win versus expectation of no win, (con3) expectation of high win (1 euro) versus expectation of low win (20 cents), and (con4) outcome: win trials versus omission trials. Regressors were evaluated in their regular and inverted form (e.g. con4/inverted, outcome: omission trials vs. win trials). Analyses of the single-participant data averaged for the two runs and a random effects analysis of the group of 12 participants were computed (threshold $p < 0.001$, minimum cluster size 50 mm^3). For the analysis of the signal time-course data, functional regions of interest (ROIs) of the activations were defined. To ensure that the single-participants' peak voxels were contained, the ROIs were defined at a less conservative threshold of $p < 0.005$ (random effects analyses). Averaged blood-oxygenation-level-dependent contrast time series of all voxels within a predefined region (calculated as percent change from the mean of overall intensity) were extracted. Statistical analyses were performed using STATISTICA 6.0. To examine a significant signal decrease owing to omission of reward, we performed a two-way within-participant ANOVA for repeated measures with time (scans) and outcome (win trial/omission trial) as factors and post-hoc Fisher tests ($p < 0.05$) for each scan.

RESULTS

Behavioural responding: In 99% of the trials, participants pressed the correct button within the required time. Reaction times were significantly faster in high-win trials (509 ms) than in low-win (535 ms; $p < 0.01$) or no-win trials (541 ms; $p < 0.01$).

Functional magnetic resonance image results: Regions involved in reward expectation: The analyses for the overall effect of expectation (con1) revealed increased activation in the left anterior insula, dorsal striatum and ventral tegmental area (Table 1). The more detailed analyses showed increased activation in bilateral ventral striatum for expectation of high win relative to expectation of low win (con3) and for expectation of win (independent of amount) relative to expectation of no win (con2) in the right ventral striatum. Analyses of time courses revealed a parametric pattern for rising amounts of money expected in the ventral striatum (Fig. 1). Conjunction analyses of the regressors con1 and con3 confirmed that activation in ventral striatum and also in left insular cortex was specific to the expectation period in comparison with the outcome phase. Inverted regressors con1–con3 revealed no significant activation.

Regions involved in receipt or omission of expected reward: The analysis of regressor con4 (outcome: win trials vs. omission trials) revealed no significant activation. The inverted regressor (omission trials vs. win trials) delivered significantly increased activation in the right anterior insula and the adjacent right ventral prefrontal cortex (RVPFC) and in the anterior cingulate cortex for omission relative to receipt of reward.

Functional regions of interest time-course analyses: Analyses of the time courses extracted from the ventral striatum ROIs (Fig. 1) revealed a parametric increase of activation for the three expectation conditions.

The right insula ROI showed a rise of activation in the insular cortex during the expectation period but an even further increase in the outcome phase specifically in omission

trials. RVPFC showed an increase in activity at a later period of the experiment than the anterior insula even more specifically related to the outcome phase of omission trials (Fig. 1).

Analyses of the time courses revealed a significant effect of outcome and time for the left [$F(11,121)=2.19$; $p<0.019$] and right [$F(11,121)=3.42$; $p<0.0004$] ventral striatum ROI in the high-win trials with significant post-hoc tests for scan 10 and 11 (Fig. 2), that is, decreased activity in trials with notification of omission of reward relative to trials with notification of receipt of reward (win). This effect was not observed in low-win trials.

Table 1. Group maximum *t*-values and Talairach coordinates (*x*/*y*/*z*) of all activation foci found for the contrast regressors (con1–con4) of the random effects analysis at $p<0.001$ uncorrected for multiple comparisons.

Condition/region		*x*/*y*/*z*	*t*-Value
con1: Expectation versus rest of the trial			
Anterior insula	L	−27/19/13	7.29
Dorsal striatum	L	−15/5/13	6.19
Ventral tegmentum	M	−3/−18/−2	8.78
con2: Expectation: win versus no win			
Ventral striatum	R	10/1/7	6.07*
con3: Expectation: high win versus low win			
Anterior insula/inferior frontal gyrus	L	−33/21/3	7.01
Ventral striatum	L	−10/6/5	5.66
	R	9/3/4	4.59
Occipital gyrus	R	18/−96/8	7.45
con4/inverted: Outcome: omission versus win			
Anterior insula	R	31/19/14	7.85
Inferior frontal gyrus	R	55/15/11	6.37
Anterior cingulate cortex	R	15/44/11	6.59

Only activations with a minimum cluster size of 50 mm^3 were included.
*Significant only at $p<0.0025$.

DISCUSSION

Under the assumption of an allocentric and an egocentric effect of the omission of reward, we explored activation within two neuronal systems, the dopaminergic reward system and brain regions previously found to mediate emotional distress. We found a specific pattern of activation in dopaminergic brain regions as potential correlates of the allocentric effect in successfully replicating prior findings in fMRI studies. Our findings support the notion that the ventral striatum is particularly recruited by anticipation of monetary reward [7] and that increasing ventral striatal response is associated with cumulative amount of money expected [5]. In addition to that, we found that bilateral ventral striatal activity was suppressed when anticipated rewards were not obtained relative to when rewards were received. This is consistent with reports of monkey dopamine neurons that show a phasic decrease in neuronal activity at the time when expected rewards fail to appear [15] and with prior fMRI findings [7]. This pattern of activation has been suggested to represent the coding of errors in the prediction of reward. It resembles the teaching signals employed in computational learning models [16] and, therefore, dopaminergic activation, especially in the ventral tegmental and striatal brain areas, has been interpreted as an important basis of learning.

But as anyone knows, the omission of a reward can lead not only to behavioural changes and learning but, usually, also to emotional distress called frustration. As potential correlates of this egocentric effect, we found increased activation in the anterior insular cortex and RVPFC, which are parts of the pain processing system [17] when comparing omission of reward with receipt of reward. According to the prior findings [10,11] we interpret the activation in RVPFC

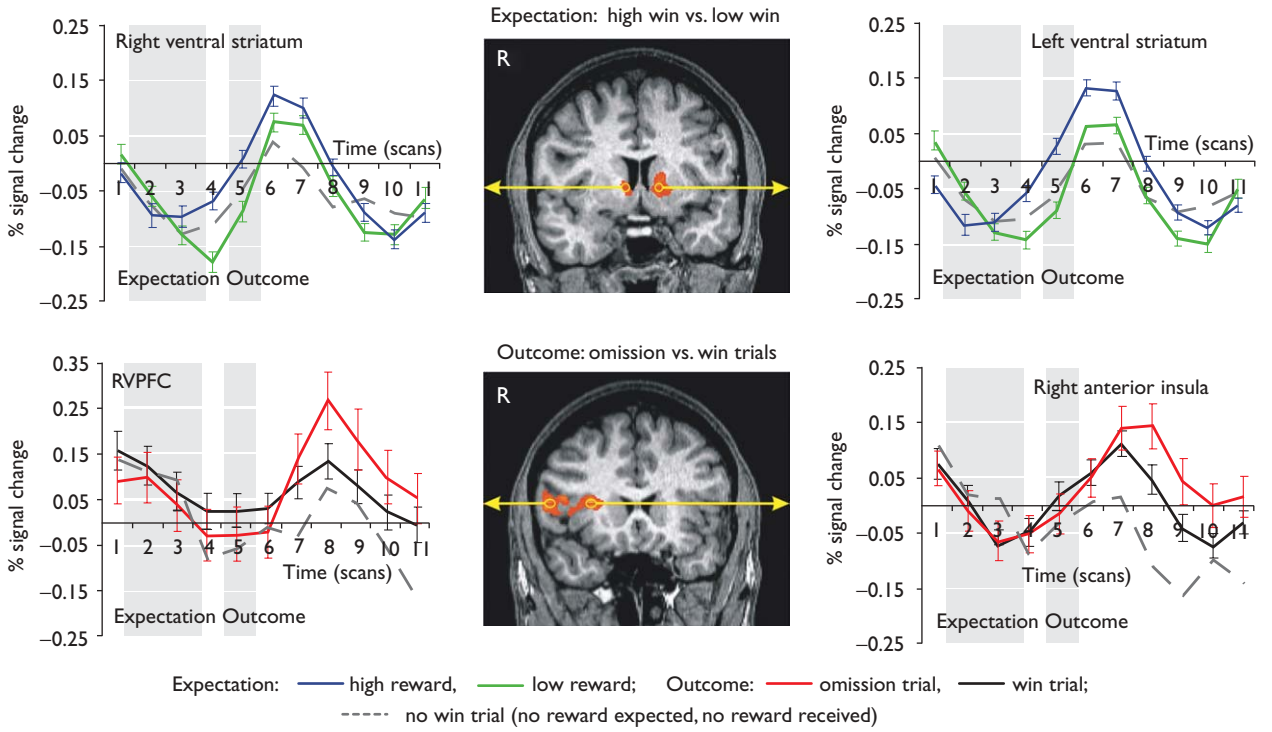

Fig. 1. Functional magnetic resonance imaging results for the following contrasts: (con3) 'Expectation: high win (1 euro) versus low win (20 cents)' (upper part) and (con4) 'Outcome: win trials versus omission trials' (lower part). Time courses highlight the contrasts in the right and left ventral striatum region of interest (ROI) and in the right anterior insula and right ventral prefrontal cortex (RVPFC) ROI. R=right.

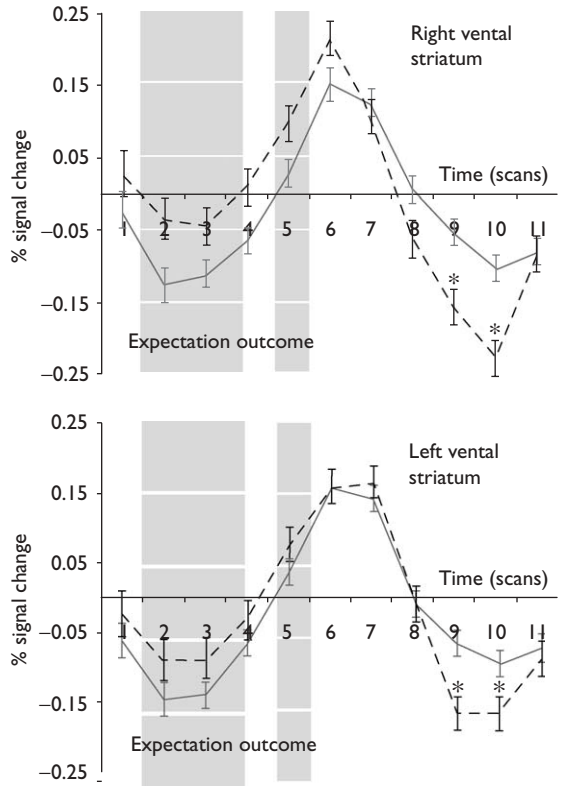

Fig. 2. Time-course plots in the left and right ventral striatum for the condition with a potential gain of 1 euro (high-win condition). Separate plots distinguish the two different outcomes [dashed line: omission of reward; straight line: receipt of reward (win)]. *Significant difference between the two conditions in the post-hoc Fisher test at $p < 0.05$.

and the right anterior insula as parts of a system processing not only physical but also emotional pain. Both areas have been implicated in regulation or inhibition of pain distress and negative affect [18,19]. Activation in RVPFC was associated with diminished self-reported distress after social exclusion, and an important role of this brain area when coping with hurt feelings owing to social exclusion has been suggested [10]. Exclusion from social interaction and the upcoming feelings can be interpreted as frustration. Our results suggest that RVPFC might play a similar role when coping with feelings of frustration without a social context. This supports the notion of a specific role for right prefrontal cortex in coping with negative emotions [20]. Also, the adjacent right anterior insular cortex is a region involved in the processing of physical and emotional pain [11] and therefore a potential region for processing frustration as the emotional reaction to the omission of a reward. Internally generated sadness was previously associated with activation in the anterior insular cortex, and a role for this brain area in generating emotional responses to distressing interoceptive stimuli has been inferred [21]. In investigations of the reward system, increased activity of the bilateral anterior insula has also been found to be related to punishing feedback, especially preceding a switch of behavioural strategies [22]. Punishment is more than pure omission of reward, but when employed as the opposite of reward, as in the respective study, one of the processes invoked may be frustration. And the feeling of frustration, more than cool reasoning, might be a trigger for changing behaviour.

CONCLUSION

According to our hypotheses, we found activation within two distinct neural systems: the dopaminergic reward system, mediating learning signals and parts of the pain processing system, mediating emotional distress. We interpret the right anterior insula and adjacent RVPFC as neuronal correlates of processing frustration.

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