ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 36 (2007) 1253–1262

Different neural systems adjust motor behavior in response to reward and punishment

Jana Wrase,[a,1] Thorsten Kahnt,[a,1] Florian Schlagenhauf,[a] Anne Beck,[a] Michael X. Cohen,[b,c] Brian Knutson,[d,1] and Andreas Heinz[a,*,1]

[a]*Department of Psychiatry, Charité – Universitätsmedizin Berlin (Charité Campus Mitte), Charitéplatz 1, 10117 Berlin, Germany*
[b]*Department of Epileptology, University of Bonn, Germany*
[c]*Department of Psychology, University of California, Davis, CA, USA*
[d]*Department of Psychology, Stanford University, CA, USA*

Received 27 November 2006; revised 27 March 2007; accepted 2 April 2007
Available online 5 April 2007

Individuals use the outcomes of their actions to adjust future behavior. However, it remains unclear whether the same neural circuits are used to adjust behavior due to rewarding and punishing outcomes. Here we used functional magnetic resonance imaging (fMRI) and a reward-providing reaction time task to investigate the adaptation of a simple motor response following four different outcomes (delivery versus omission and monetary gain versus loss). We found that activation in the thalamus and insula predicted adjustments of motor responses due to outcomes that were cued and delivered, whereas activation in the ventral striatum predicted such adjustments when outcomes were cued but omitted. Further, activation of OFC predicted improvement after all punishing outcomes, independent of whether they were omitted rewards or delivered punishments. Finally, we found that activity in anterior cingulate predicted adjustment after delivered punishments and activity in dorsal striatum predicted adaptation after delivered rewards. Our results provide evidence that different but somewhat overlapping circuits mediate the same behavioral adaptation when it is driven by different incentive outcomes.

Keywords: fMRI; Instrumental learning; Behavior adaptation; Orbitofrontal cortex; Striatum; Anterior cingulate

Introduction

Motivation is crucial for survival: it engages individuals to seek sustenance and opportunities for reproduction and helps them avoid danger (e.g. Di Chiara, 2002; Everitt and Robbins, 2005). Thus, a fundamental function of neural circuits that support motivation is to regulate approach and avoidance behavior in response to environmental cues (Berridge and Robinson, 1998; Panksepp, 1998). The consequences of these responses cause an adaptation of behavior towards a reward-maximizing and punishment-minimizing optimum. This adjustment occurs in decisions about behavioral options as well as in simple motor processes such as movement and coordination. An open question is whether these adaptations involve the same brain structures for different incentive outcomes such as delivered and omitted rewards and punishments.

It has long been established that incentives promote behavioral adaptation (Skinner, 1953). This phenomena is hypothesized to reflect the workings of a reinforcement learning system that uses error signals to correct and dynamically adjust performance (Holroyd and Coles, 2002; Pagnoni et al., 2002). However, the precise neural substrates of such behavioral adaptation, and whether rewards and punishments are used to adjust behavior in the same way, remain unclear. Recently, fMRI studies have begun to examine how brain activation can predict complex decision making for future behavior (Cohen and Ranganath, 2005; Haruno et al., 2004; Kuhnen and Knutson, 2005). Although these studies investigated the ability of brain activation to predict future decision making, they examined risky decisions that likely require complex cognitive and emotional processing. Here, we examined whether such predictive activations are present in a simple reward motivation task (Knutson et al., 2001).

While there is broad evidence that some regions including the amygdala and orbitofrontal cortex (OFC) play a fundamental role in encoding, updating and maintaining reward values and therefore are involved in processing of both reward and punishment (Baxter and Murray, 2002; Gottfried et al., 2003; Pickens et al., 2003), recent neuroscience research also suggests that rewarding and punishing outcomes may be processed by distinct neural circuits (Yacubian et al., 2006). For instance, circuits including the striatum and mesial prefrontal cortex (MPFC) may facilitate reward-related behavioral learning (Haruno et al., 2004; Knutson et al., 2003; O'Doherty et

* Corresponding author. Fax: +49 30 450517921.
E-mail address: andreas.heinz@charite.de (A. Heinz).
[1] Equal contribution.
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2007.04.001

al., 2004), whereas circuits including the lateral OFC, insula and anterior cingulate may facilitate punishment-related behavioral adjustments (Frank et al., 2005; Gottfried and Dolan, 2004; O'Doherty et al., 2003). Therefore, we hypothesized that different mechanisms might support dynamic behavioral adjustments based on different incentive outcomes. Because neural activation to incentive outcomes strongly depends on preceding cues (Nicola et al., 2004; Schultz et al., 1997), we further hypothesized that different neural circuits also process motor adjustment depending on whether the cued outcome is delivered or omitted.

We used event-related fMRI to examine activations during a monetary incentive delay task in which subjects were cued to rapidly respond to gain or avoid losing money (e.g. Juckel et al., 2006). This task represents four possible consequences of behavior (Fig. 1b): (1) delivery and (2) omission of cued gains, and (3) delivery and (4) omission of cued losses. We examined the influence of feedback on subsequent performance to investigate whether there is an adaptation in motor behavior depending on these outcomes. Furthermore, in order to identify brain circuits that facilitate basic motor responses as a function of these different outcomes, activation during these consequences was correlated with individual differences in improvements in reaction time in the subsequent trial.

Materials and methods

Subjects

Fourteen physically and psychologically healthy right-handed male subjects (mean age 39.9; SD 10.3) were included in the study. Written informed consent was obtained from all subjects after the procedures had been fully explained. The study was approved by the Ethics Committee of the Charité University Medicine Berlin. Exclusion criteria were family history of psychiatric disorders and past history of dependency or current abuse of drugs. Half of the subjects were smokers.

Monetary incentive delay (MID) task

A "monetary incentive delay" (MID) task as previously described by Knutson et al. (2001) was used to examine brain activation during trials in which subjects anticipated potential monetary gain, loss or no consequences. The subjects' monetary gain depended on their performance in a simple reaction time task (see Fig. 1a).

In each trial, subjects saw one of seven geometric figures ("cue"; 250 ms), which indicated that they could either gain or prevent losing different amounts of money (3.00, 0.60 or 0.10 €) via a fast button press while a target cue (white square) was presented. Before the target was presented, a variable interval (delay: 2250, 2500 or 2750 ms) was implemented. After target presentation, feedback appeared ("feedback"; 1650 ms), informing subjects that they had won or lost money and indicating their cumulative total. An adaptive algorithm for target duration ensured in an online manner that subjects succeeded on an average of 67% of trials. The inter-trial interval was 4000 ms. Subjects performed two sessions, each consisting of 72 trials (27 potential gain, 27 potential loss and 18 neutral trials) that were ordered randomly. Money was shown in cash to the subjects before entering the scanner and they were informed that they would receive the money from the session in which they performed best. During structural scans, subjects completed a short practice version of the task in order to ensure that they understood the task.

Probability of performance improvement

The MID task yields four possible feedback conditions: (1) gain cue and gain outcome (GG), (2) gain cue and nongain outcome (GN), (3) loss cue and loss outcome (LL) and (4) loss cue and nonloss outcome (LN) (Fig. 1b). In order to assess the adaptation of behavior depending on feedback, we calculated each subject's ability to use feedback to adjust subsequent reaction time. For each of the four outcomes, *x*, the number of trials in which the outcome

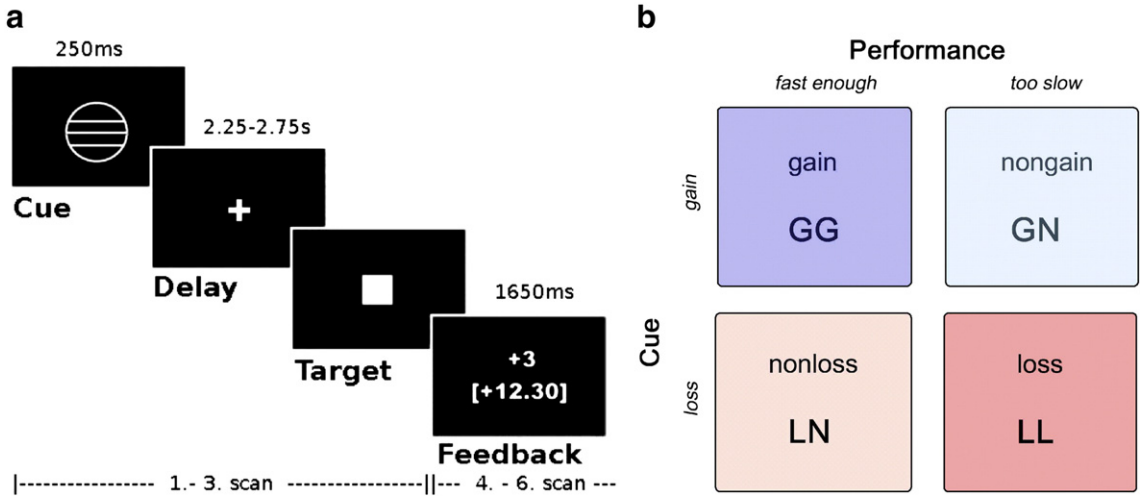

Fig. 1. (a) Example trial in the monetary incentive delay task. In each trial a cue indicates the amount of money that can be gained or lost. Subjects had to react to the white target square in order to gain or avoid losing money. Subsequently, feedback is given. (b) Four possible outcomes (rewarding versus punishing × delivered versus omitted) depending on cue (gain versus loss) and performance (fast enough versus too slow). (1) GG: cued monetary gain and fast enough button press > gain received; (2) GN: cued monetary gain and button press too slow > no gain received; (3) LL: cued monetary loss and button press too slow > loss received; (4) LN: cued monetary loss and fast enough button press > no loss received.

x in the current trial t was followed by a reduced reaction time in the subsequent trial was divided by the total number of trials with this outcome. In brief, the probability of performance adjustment (pa) after a certain type of feedback x is defined as:

$$\mathrm{pa}(x) = \frac{\sum_{t}^{n\mathrm{trials}_x} \left\{ \begin{array}{ll} 1 & \text{if } \mathrm{RT}_{t+1} < \mathrm{RT}_t \\ 0 & \text{otherwise} \end{array} \right\}}{n\mathrm{trials}_x}$$

with $x \in$ [GG, GN, LL, LN], and $n\mathrm{trials}_x$ is the number of trials in condition x. Thus, a pa value of 1.0 indicates that the subject responded faster on every trial $t+1$ relative to trial t for that condition; and a pa value of 0.0 indicates that the subject responded slower on every trial $t+1$; finally, a pa value of 0.5 indicates that subjects were faster on one half of trials $t+1$ and slower on the other half. Because mean reaction time was significantly slower in trials with the neutral condition relative to the other conditions (see Results), we included only trials that were *not* followed by the neutral condition. Thus, we computed four individual scores (pa (GG), pa(GN), pa(LL), pa(LN)) for each subject, representing the degree to which subjects were faster to respond on trial $t+1$ after each type of feedback. In other words, these indices represent the degree of behavioral adaptation by outcome type for each subject. This could be interpreted as sensitivity to feedback that is associated with behavioral adaptation. These scores were not inter-correlated (all p's >0.17, Bonferroni corrected for multiple comparisons), suggesting that they reflect independent processes.

fMRI acquisition

Functional magnetic resonance imaging (fMRI) was performed on a 1.5-T scanner (Magnetom VISION Siemens®) equipped with a standard circularly polarized head coil (CP-Headcoil) using gradient echo–echo planar imaging. We used the following parameters: GE-EPI, TE 40 ms, flip angle 90°, matrix 64×64, voxel size 4×4×3.3 mm. Eighteen slices were collected every 1.87 s approximately parallel to the bicommissural plane, covering the inferior part of the frontal lobe, the whole temporal lobe and large parts of the occipital region. The paradigm consists of two sessions, resulting in a total of 144 trials (54 gain trials, 54 loss trials, 36 trials with no outcome). Six volumes were acquired per trial in addition to 9 volumes in the beginning and in the end, resulting in a total of 450 volumes per session. The two sessions were performed subsequently without moving the subjects in the scanner. For anatomical reference a 3D MPRAGE (magnetization prepared rapid gradient echo, TR 9.7 ms; TE 4 ms; flip angle 12°; matrix 256×256, voxel size 1×1×1 mm) image was acquired. Head movement was minimized using a vacuum pad.

fMRI data analysis

Functional MRI data were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Slice time correction was conducted to adjust for time differences due to multislice imaging acquisition. To correct for between-scan movements and to remove signals correlated with head motion, sinc interpolation was used to realign all volumes to the middle volume. The structural 3D data set was coregistered to the first T2* image. The coregistered structural image was spatially normalized to the standard template provided by the Montreal Neurological Institute (MNI-Template) using an automated spatial transformation (12-parameter affine transformation followed by nonlinear iterations using 7×8×7 basis functions) (Ashburner and Friston, 1999). The estimated transformation parameters were applied to all functional images, interpolating to a final voxel size of 3×3×3 mm^3 and the normalized images were smoothed with a Gaussian kernel (full width at half maximum 6 mm) in order to capture activation in small subcortical structures (e.g. the nucleus accumbens) as well as in cortical areas.

The pre-processed functional MRI data were then analyzed in the context of the general linear model (GLM) approach, using a two-level procedure. Changes in the BOLD response can be assessed by linear combinations of the estimated GLM parameters (beta values) and are contained in the individual contrast images (equivalent to percent signal change or effect size). This analysis was performed by modeling the seven cue conditions and the five feedback conditions (four incentive outcomes and one after neutral cues) separately as explanatory variables convolved with the gamma-variate function described by Cohen (1997) and similar to Knutson et al. (2001) and Breiter et al. (2001). Realignment parameters were included as additional regressors in the statistical model.

To investigate the activation of different anticipatory events and outcomes, the estimated beta-values were used to compute individual contrast images for the contrasts "gain cue>no outcome cue", "loss cue>no outcome cue", "gain cue>loss cue", "feedback of gain>nongain" (GG>GN), "feedback of nongain>gain" (GN>GG), "feedback of loss>no loss" (LL>LN) and "feedback of no loss>loss" (LN>LL). In fact, positive values (activations) in the GN>GG and LN>LL contrasts are negative values (deactivations) in the GG>GN and LL>LN contrasts, respectively; however, we report them separately to facilitate interpretation. Comparison of outcomes with their opposite outcomes controls for influences of different anticipation modes. For instance, the GG>GN contrast yields only activations elicited by monetary gain and is not contaminated by activation related to anticipation. The same is true for LL>LN, GN>GG and LN>LL. The individual contrast images of all subjects were included in a second level random effects analysis, comparing within-group activation with a one-sample t-test, at the $p<0.001$ level, uncorrected and a voxel threshold of $k=5$. We searched for regions previously observed in experiments utilizing the MID task (e.g. ventral striatum and MPFC, Knutson et al., 2001; Knutson et al., 2003) to verify that the results replicated for the entire group using SPM2 small volume correction (SVC) with publication-based anatomical ROIs (http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html) with false discovery rate (FDR) correction at a $p<0.05$ level.

To detect the association of brain activation in response to feedback with future motor adjustment, individual contrast images of the four feedback contrasts (GG>GN, GN>GG, LL>LN and LN>LL) were correlated with the corresponding probability of performance improvement (pa(GG), pa(GN), pa(LL) and pa(LN)). This analysis was designed to reveal brain regions in which activation during feedback predicted the probability of a subsequent faster response. We assessed correlations using SPM2 simple regression analysis and an omnibus threshold of $p<0.001$ uncorrected.

Anatomical localizations were carried out by overlaying the statistical maps on a normalized structural image averaged across subjects and with reference to an anatomical atlas (Duvernoy, 1999). Additionally, MNI-coordinates were transformed in the Talairach-space and corresponding areas were identified with reference to the atlas provided by Talairach and Tournoux (1988).

Results

Behavioral data

Due to the pre-programmed adaptive algorithm implemented in the MID task, subjects succeeded (i.e. responded within the target duration) in 65.21% of potential gain trials and in 66.53% of potential loss trials. They gained an average of €17.82 per session. Reaction times (mean 247.79 s; SEM 2.19) differed between trial types. Mean reaction times across trials and subjects are shown in Fig. 2a. A one-way ANOVA revealed a significant main effect of cue condition ($F=28.85$; $p<0.001$). Post hoc t-tests (Bonferroni corrected for multiple comparisons; $p<0.001$) demonstrated faster reaction times for incentive trials (i.e. gain or loss cue) compared to the neutral trials (no outcome cue), but did not differ significantly as a function of different incentive magnitudes (Fig. 2a).

Neural activity during gain and loss cues

The group analysis replicated findings of prior studies (Breiter et al., 2001; Delgado et al., 2000; Knutson et al., 2001) revealing ventral striatal activation during anticipation of monetary gain versus no outcome (left [−15 6 0], $t=12.48$; right [18 6 0], $t=10.49$, Fig. 3a, Table S1). Furthermore, we also observed significant signal change during anticipation of monetary loss versus no outcome in the ventral striatum (left [−12 12 0], $t=9.55$; right [15 9 0], $t=5.87$, Fig. 3b, Table S1).

Neural responses to actual outcome (feedback)

We also replicated findings of prior studies showing cortical and subcortical activation during feedback of monetary gain (Knutson et al., 2003). There was significant activation for the condition "gain versus nongain outcome" (GG>GN) in the left ventral striatum ([−12 9 −6], $t=4.25$) and the right MPFC (BA 32, [6 42 0], $t=6.16$, Figs. 3d–e, Table S2). To confirm that these results were specific to gain outcomes and not a general effect of outcome receipt, we conducted the comparison of GG>GN versus LL>LN. This contrast revealed the same brain regions at a slightly lower t-value.

As the volume of interest (VOI) analysis in Fig. 3 indicates, the MPFC finding seems to be due to increased activation during gain outcomes as well as deactivation during nongain outcomes (cf. Knutson et al., 2003). Similar to findings in other studies using the MID (Knutson et al., 2003; Knutson and Cooper, 2005) but contrary to results of studies using different reward-providing paradigms (Kim et al., 2006; Pessiglione et al., 2006), no significant activation was found for the other three contrasts "feedback of no gain>gain" (GN>GG) or feedback of avoided or sustained losses (LN>LL and LL>LN). These results verified that our paradigm produced the expected pattern of results and set the stage for the following adaptive behavior analyses.

Behavioral adjustment

For the correlation analysis we first had to ensure that feedback of different outcomes had an impact on subsequent reaction time (RT), i.e. that RT in subsequent trials and therefore the probabilities of performance improvement differed as a function of incentive feedback. Differences in RT (RT in $t+1$ minus RT in t) after different outcomes are shown in Fig. 2b. A repeated-measures ANOVA of the RT differences revealed a significant main effect of outcome condition ($F(3,36)=19.4$, $p<0.001$). Post hoc analyses showed significant differences between RT differences after rewarded and nonpunished versus punished and nonrewarded trials. On average, RT decreased after trials in which performance was inadequate, whereas RT only slightly increased after adequate performance. As can be seen in Fig. 2b, the decrease in RT after punished trials was more pronounced than the increase after rewarded trials.

A repeated-measures ANOVA applied on the probabilities of performance improvement revealed a main effect of feedback condition ($F(3,39)=14.3$, $p<0.001$, Fig. 2c). The likelihood that the outcome was followed by a decrease in RT for the subsequent trial was significantly greater in trials in which the RT was too slow, i.e. the outcome was punishing compared to trials in which subjects responded fast enough, i.e. that were followed by a rewarding outcome (all p's<0.01 except the comparison pa(LL)–pa(NL), which was only in trend $p=0.095$, Bonferroni corrected).

The probabilities of performance improvement after rewarded trials (pa(GG) and pa(LN)) were beneath 0.5, whereas those after punished trials (pa(GN) and pa(LL)) were above 0.5 (Fig. 2b). This means that after rewarding outcomes, where subject's speed was already adequate, subject's performance was steady or even slightly decreased. In punished trials the negative outcome seems to inform the subject that s/he is responding too slowly and therefore needs to speed up on the next trial. In this sense, adjustment is not only a decrease of RT but also a settling-down or even an increase after

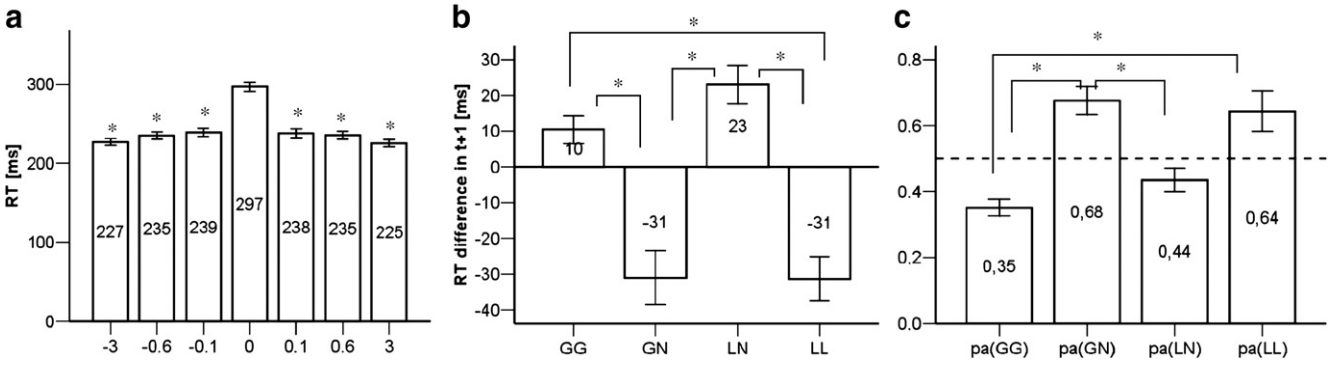

Fig. 2. (a) Reaction times (ms) as a function of cue. Asterisks denote significant paired comparisons between incentive versus neutral (no outcome) trials at the $p<0.001$ level (Bonferroni corrected). (b) Reaction time differences (ms) between trial t and $t+1$ as a function of incentive outcome of trial t. Asterisks denote significant paired comparisons at the $p<0.01$ level (Bonferroni corrected). (c) Probabilities of performance improvement as a function of incentive outcomes. Asterisks denote significant paired comparisons at the $p<0.01$ level (Bonferroni corrected). (a–c) Error bars indicate SEM.

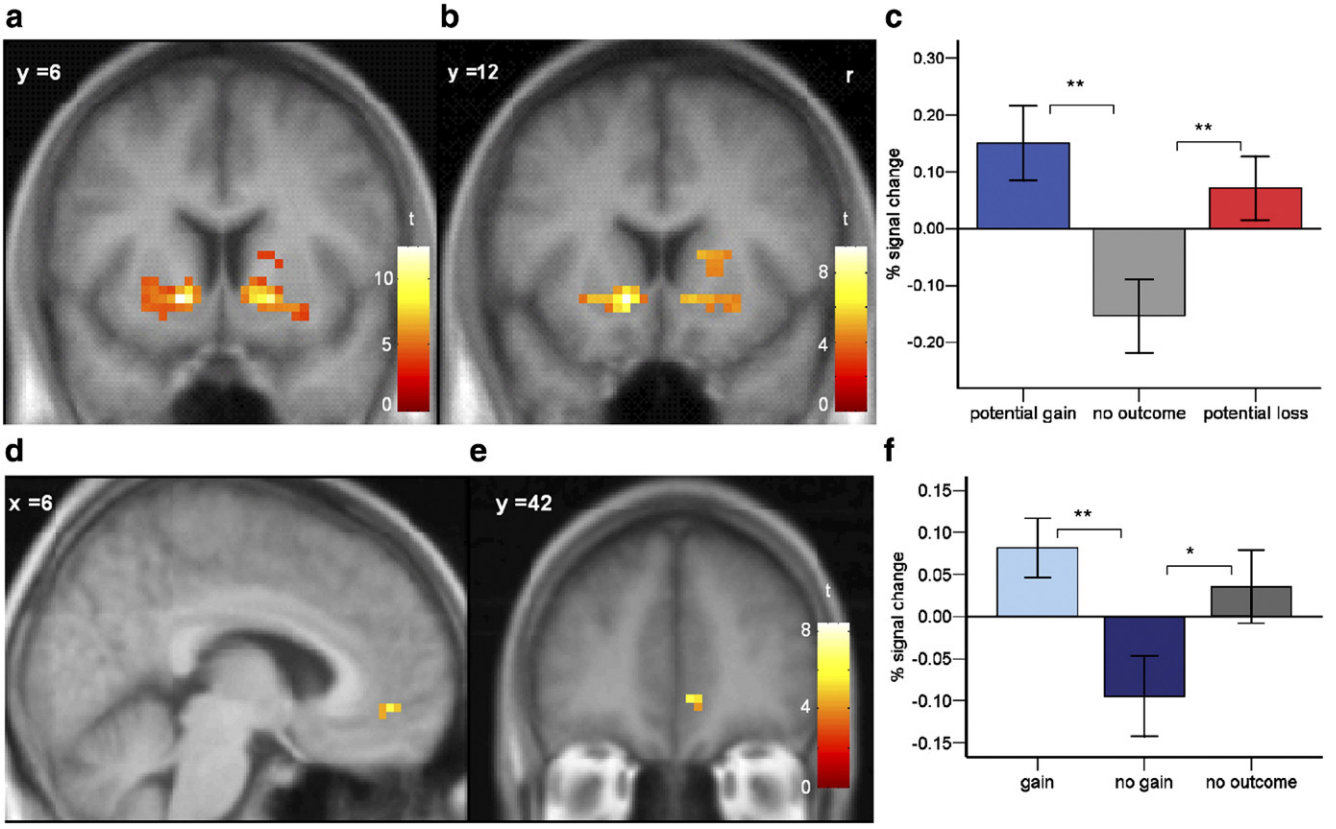

Fig. 3. Activation in bilateral ventral striatum during anticipation of potential monetary gain (a) and potential monetary loss (b), and activation in MPFC during feedback of monetary gain compared to nongain (GG>GN) (d, e). The threshold is set at $p<0.001$ uncorrected for illustration; t maps are overlaid on a normalized structural image averaged across all subjects. Percent signal change from baseline in the left ventral striatum (c) and MPFC (f) averaged over trials and subjects (VOI consists of active cluster at the $p<0.001$ level). Error bars indicate SEM; asterisks denote significant paired comparisons between incentive versus neutral (no outcome) trials at the *$p<0.01$ and **$p<0.001$ levels.

such responses that were already adequate and become rewarded. These analyses showed that subjects did adjust their behavior according to different outcomes. In our next set of analyses, we examined which brain regions might underlie such motor adjustment processes.

Correlation analysis

Probability of performance improvement (increased motor speed) was correlated with each type of feedback. Because we were interested in examining effects of outcome evaluation rather than anticipation, we correlated the probability of performance improvement pa(x) after each type of outcome (GG, GN, LL, LN) with parameter estimates of the GG>GN, GN>GG, LL>LN and LN>LL contrasts at each voxel. In these contrasts, activity related to anticipation of outcomes is subtracted out. This analysis thus identifies brain regions in which activity in response to incentive outcomes was associated with the probability of performance adjustment on the following trial.

We first investigated how activations predicted performance adjustments after delivery of cued gain by correlating pa(GG) with the contrast images GG>GN. Activation in response to gain feedback correlated with probability of performance improvement in the next trial in the right insula ([42 −9 3] $r=0.85$; see Fig. 4a), bilateral dorsal putamen (left [−18 6 12], $r=0.84$; right [27 −12 12], $r=0.76$) and the left thalamus ([−15 −6 12], $r=0.83$; Table 1).

Activation in response to omission of cued gain (GN>GG) correlated with the probability of performance improvement in the next trial pa(GN) in the lateral OFC (left BA47, [−42 33 −6], $r=0.85$; right BA47, [51 30 0], $r=0.82$; see Fig. 4b), left ventral striatum ([−9 9 −3]; $r=0.77$) and cuneus (Table 1).

Neural activation in response to delivery of cued loss feedback (LL>LN) correlated with performance adjustment in the next trial pa(LL) in the ACC (BA32 [−12 42 9], $r=0.83$; see Fig. 4c), insula (BA 13 [48 −6 9], $r=0.80$), lateral OFC (right BA11 [30 45 −3], $r=0.85$), thalamus ([6 −36 15], $r=0.78$) and other regions (Table 1).

Neural activation in response to omission of cued loss feedback (LN>LL) correlated with the probability of performance improvement in the next trial pa(LN) only in the left ventral striatum ([−12 3 −3], $r=0.83$; see Fig. 4d, Table 1).

Discussion

Here we show that subjects use feedback about their actions to adjust their future motor behavior. Further, this adaptation in response to incentive outcomes correlated with activation in brain regions implicated in incentive processing. The findings are consistent with the notion that these regions play a critical role in using incentive outcomes to adjust motor responses. While activity in some regions correlated with motor adaptation after rewarding outcomes (e.g. the dorsal striatum), activity in other regions

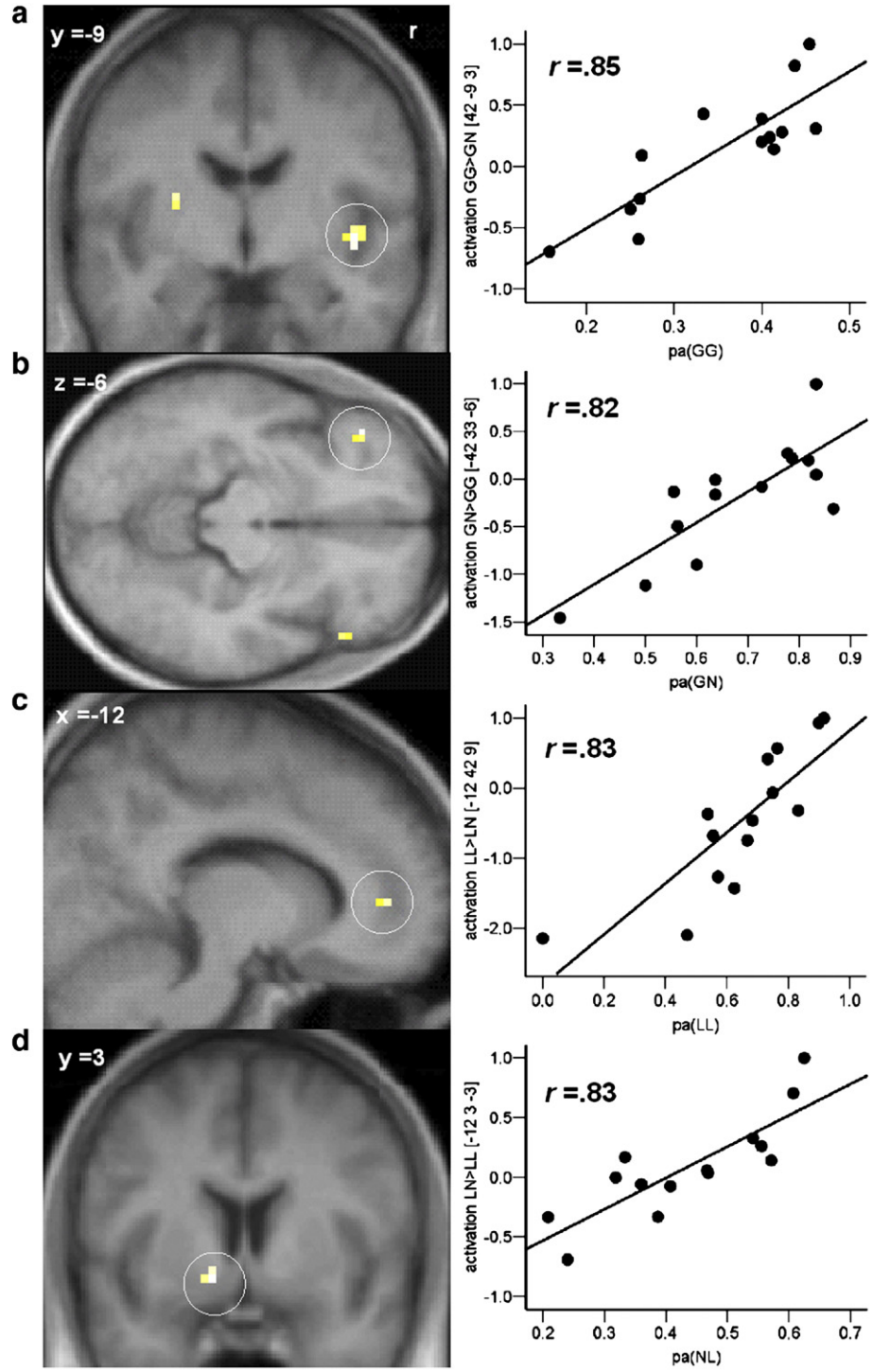

Fig. 4. Brain regions in which neural activity is significantly correlated with the probability of performance improvement following different outcomes (pa(GG), pa(GN), pa(LL), pa(LN)) in the respective feedback contrasts (GG>GN, GN>GG, LL>LN, LN>LL). (a) Correlation between pa(GG) and activity in right insula ([42 −9 3] r=0.85) for the contrast GG>GN. (b) Correlation between pa(GN) and activity in OFC (left BA47, [−42 33 −6], r=0.85; right BA47, [51 30 0], r=0.82) for the contrast GN>GG. (c) Correlation between pa(LL) and activity in ACC (BA32 [−12 42 9], r=0.83) for the contrast LL>LN. (d) Correlation between pa(LN) and activity in left ventral striatum ([−12 3 −3], r=0.83) for the contrast LN>LL. Activations are shown at the p<0.001 level uncorrected for illustration; t maps are overlaid on a normalized structural image averaged across subjects. The corresponding scatter plots are displayed. Abscissas contain the respective probabilities; ordinates the mean activation in the respective cluster qualified at the maximum value.

correlated with motor adaptation in response to punishing outcomes (e.g. the anterior cingulate and OFC), and activity in still other regions correlated with motor adaptation in response to both types of incentive outcomes but depending on whether the cued outcome was delivered or omitted (e.g. insula, thalamus and ventral striatum). These findings suggest that behavioral adaptation is not

Table 1
BOLD signal associated with behavior adjustment

Region		BA	MNI coordinates			Peak *t*	Correlation (*r*)
			x	*y*	*z*		
Gain vs. nongain feedback (GG>GN) correlated with the probability of faster reaction time in the next trial (pa(GG))							
Left	Dorsal striatum (putamen)		−18	6	12	5.28	.84
Right	Dorsal striatum (putamen)		27	−12	12	4.01	.76
Right	Insula		42	−9	3	5.51	.85
Left	Thalamus		−15	−6	12	5.18	.83
Nongain vs. gain feedback (GN>GG) correlated with the probability of faster reaction time in the next trial (pa(GN))							
Left	Ventral striatum		−9	9	−3	4.16	.77
Left	Orbitofrontal cortex	47	−42	33	−6	5.47	.84
Right	Orbitofrontal cortex	47	51	30	0	5.02	.82
Left	Cuneus	18	−12	−81	18	4.35	.78
Loss vs. nonloss feedback (LL>LN) correlated with the probability of faster reaction time in the next trial (pa(LL))							
Left	Anterior cingulate	32	−12	42	9	5.10	.83
Right	Anterior cingulate	24	6	33	9	4.03	.76
Left	Insula		−45	−6	9	4.57	.80
Right	Insula		45	−6	15	4.35	.78
Right	Orbitofrontal cortex	11	30	45	−3	5.69	.85
Right	Thalamus		6	−36	15	4.29	.78
Left	Posterior cingulate	29	−6	−39	15	4.10	.76
Left	Angular gyrus	39	−42	−66	33	4.50	.79
Left	Superior temporal gyrus	39	−48	−60	30	4.08	.76
Left	Middle temporal gyrus	39	−33	−57	24	4.03	.76
Nonloss vs. loss feedback (LN>LL) correlated with the probability of faster reaction time in the next trial (pa(LN))							
Left	Ventral striatum		−12	3	−3	5.22	.83

Peak voxel coordinates, $p<0.001$ uncorrected.

governed by a unitary mechanism; instead, distinct and convergent mechanisms may promote adaptation to different incentives.

Behavioral adjustment

The analysis of the behavioral data suggested that reaction times were adjusted after different incentive outcomes. After incentive outcomes indicating that performance was not sufficient (GN and LL), RT was more likely to decrease in subsequent trials (i.e. pa(x)>0.5). In contrast, outcomes that informed the subject that the previous response was already adequate (GG and LN), subsequent RT did not decrease further or even increased, resulting in a mean probability of getting faster in the next trial of pa(x)<0.5. However, the decrease in RT after punishing outcomes was more pronounced than the slightly increase in mean RT after rewarding outcomes. Therefore, it seems that feedback about the current performance was meaningful to the subjects and was used to adjust behavior in a trial-by-trial manner.

Neural systems associated with behavior adjustment

To localize brain regions that may promote adaptation of motor responses as a function of incentive feedback, we correlated individual differences in the extent to which subjects adjusted subsequent motor behavior with incentive-related activation. In other words, stronger brain activations during incentive feedback were correlated with the probability of decreased reaction time in the subsequent motor response. The four possible outcomes can be fitted into a two-dimensional space demarcated by rewarding versus punishing outcomes and delivery versus omission of cued outcomes (Fig. 5). Activation in different neural circuits corresponded to the dimensions denoted in Fig. 5.

Notably, we found that lateral OFC was involved in the adaptation of behavior due to all punishing but not to rewarding outcomes. In humans, OFC lesions lead to impairments in social, moral and emotion-related behavior (Anderson et al., 1999; Anderson et al., 2006; Eslinger and Damasio, 1985), to deficits in decision making (Bechara et al., 2001) and to insensitivity to behavior consequences (Bechara et al., 1994). Recent functional neuroimaging studies revealed a role of OFC in reversal and extinction in both classical and operant conditioning tasks (Cools et al., 2002; Gottfried and Dolan, 2004; Kringelbach and Rolls, 2003; O'Doherty et al., 2003). Using fMRI in humans, O'Doherty et al. (2003) demonstrated that lateral OFC is activated in response to reversals in reward contingencies and predicts a change in behavior. Likewise, Cools et al. (2002) have shown that error feedback preceding a change in decision strategy activates lateral OFC, in contrast to error feedback that has no impact on future behavior. Our results suggest that this function of lateral OFC is not restricted to rather complex decision-making behavior but also plays a role in adjustment of simple motor responses.

In our study the anterior cingulate predicted only adaptation due to cued loss outcomes. Anterior cingulate activation has been implicated in anticipation of pain (Buechel and Dolan, 2000) and performance errors (Critchley et al., 2005b). It has been shown that the error-related negativity (ERN) as measured with EEG which is likely generated by the anterior cingulate, predicts reinforcement learning (Frank et al., 2005). In analogy with our study, Frank et al. (2005) showed that subjects who learned from negative events had

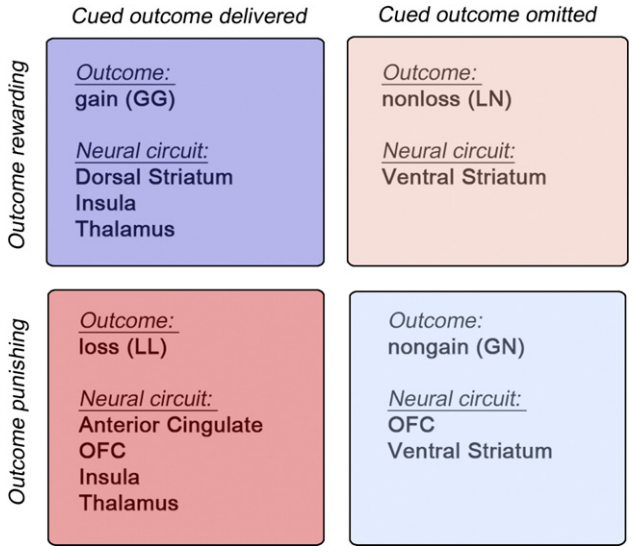

Fig. 5. Adjustment of behavior towards a maximum of reward and a minimum of punishment can be classified using the dimensions rewarding versus punishing outcomes, and cued outcome delivered versus omitted. The brain regions corresponding to these dimensions are reported in the cells.

larger ERNs that correspond to learning from punishment. Furthermore, Luu et al. (2003; 2004) found that a similar feedback-related negativity in anterior cingulate tracked affective response to the feedback and predicted subsequent performance. Source analysis suggested that the topography of the feedback-related negativity can be localized, with striking similarity to our findings, in the rostral region of the anterior cingulate. More recently, Cohen and Ranganath (2007) recorded EEG while subjects played a strategic decision-making game and found the feedback-related negativity (similar to the ERN and also thought to be generated in the anterior cingulate) predicted strategic adjustments following losses, but not following gains, suggesting that this region specifically uses punishment information in guiding behavior.

Activation in ventral striatum predicted performance improvement after rewards and punishments that were cued but omitted. According to Schultz et al. (1997), the difference between the actual and expected outcome is coded in the discharge-rate of dopaminergic neurons, which innervate the ventral striatum. If a reward is completely predicted by a preceding conditioned stimulus, midbrain dopamine neurons should only alter firing rate in response to the omission of an expected reward. In this study, ventral striatal activation was related to the probability of performance improvement during the omission of a cued reward, but also during the omission of a cued punishment suggesting a role of the ventral striatum in behavior adjustment due to the omission of cued outcomes.

Insular and thalamic activation were correlated with behavior improvement after delivery of cued rewarding and punishing outcomes. Insular activation has been documented in processing of aversive (Abler et al., 2005; Critchley et al., 2002) and also appetitive events (Bartels and Zeki, 2004), as well as in general emotional processing, perception of visceral responses and interoceptive awareness (Bermpohl et al., 2006; Critchley et al., 2004; 2005a). The actual delivery of monetary gain and loss may have incited increased arousal. These psychophysiological responses, passing through the thalamus, can be represented in the insular cortex and may influence learning and facilitate decision-making and behavioral adaptation (Critchley, 2005).

We found that dorsal striatal activation to the delivery of cued rewarding outcomes predicted faster reaction times. The dorsal striatum facilitates motor learning and habit formation and has been hypothesized to link reward outcomes to subsequent behavior (Delgado et al., 2005; Everitt and Wolf, 2002; Haruno et al., 2004; O'Doherty et al., 2004). Activation in dorsal striatum during an instrumental conditioning paradigm has been implicated in learning from reward (O'Doherty et al., 2004). Likewise, Haruno et al. (2004), using fMRI in humans, found activation in dorsal striatum to be correlated with reward-based learning in a stochastic decision task. In line with our findings, these studies support the hypothesis that dorsal striatum plays a major role in learning from the delivery of reward (i.e. positive reinforcement).

Behavioral adaptation after gain, nongain, loss and nonloss outcomes corresponds to the four different outcome conditions of instrumental conditioning. While gain and loss outcomes are cued and delivered, nongain and nonloss are cued but omitted. In behaviorist terms, gain outcomes correspond to positive reinforcement, while nongain outcomes correspond to negative punishment. Similarly, loss outcomes correspond to positive punishment, while nonloss outcomes correspond to negative reinforcement. Our findings suggest that dorsal putamen processes behavior adaptation to positive reinforcement whereas anterior cingulate activation is associated with behavior adaptation to positive punishment. Performance improvement following the omission of outcomes, that is negative reinforcement and negative punishment, is supported by ventral striatal activation. Behavior adaptation potentially recruiting instrumental conditioning mechanisms which are based on aversive consequences, i.e. positive and negative punishment, were associated with activation elicited in the lateral orbitofrontal cortex. These brain activation patterns thus support feedback-driven behavior adaptation and may contribute to the more complex processes of instrumental conditioning.

O'Doherty et al. (2004) found correlations of dorsal striatal activation with learning algorithms during positive reinforcement. This finding was replicated in the present study, which used individual differences in brain activation to predict motor adjustment, a prototypical example of instrumental conditioning. We detected further neurocircuits, which might be implicated in instrumental conditioning with negative reinforcement as well as positive and negative punishment. In the present paradigm, all incentive conditions required the same type of motor adjustment, ruling out explanations for recruitment of different circuits based on different motor demands. Even though the type of behavioral adjustment was the same for all trial types, different types of outcomes may exert different motivational demands for adjustment. However, the motivation component might vary from trial-to-trial and subject-to-subject and is therefore complex and difficult to model. Furthermore, we cannot specify the extent to which improvements in motor performance reflected instrumental learning versus more transient fluctuations in motivation. In our view, the different outcomes provide at least the conditions in which operant conditioning could occur. Since learning and motivation are always mingled, further studies are needed to clarify the specific contribution of each.

A limitation of our study is that we used a between-subject analysis, which reveals inter-individual differences in brain activation elicited by feedback that are significantly correlated with inter-individual differences in behavior adaptation; however, our approach does not reveal mechanisms underlying behavioral change in response to rewarding or punishing feedback within subjects. Our trial number per subject was too small for an intra-subject analysis: in such an intra-subject design, we would have to compare within the same condition (e.g. trials with gain cue and nongain outcome [GN]) the trials in which a subject became faster with those trials in which a subject slowed down. These contrasts appear to be underpowered for an intra-individual analysis. In contrast, using the inter-subject analysis allowed us to compare conditions with sufficient number of trials, no matter whether subjects became slower or faster due to feedback. Therefore, the results obtained with our approach reflect inter-individual differences in neuronal sensitivity to feedback that was associated with behavioral adaptation. Further studies are needed to clarify whether the same regions can be identified when a within-subject approach is used.

Conclusion

We examined the relationship between brain activation and adaptation of a simple motor response to rewarding and punishing outcomes. While one might assume a more parsimonious neural account (i.e. that a single system drives all reinforcement-guided behavioral adaptations), our results provide evidence that different

circuits mediate the same behavioral adaptation when it is driven by different incentive outcomes. In particular, ventral striatal activation was correlated with behavior adjustment after all outcomes that were cued but omitted, while insula and thalamus activation increased the probability of faster reaction times after all cued and delivered outcomes. On the other hand, lateral OFC activation was correlated with improvement of motor responses after all punishing outcomes, while anterior cingulate activation was exclusively correlated with improvement of motor responses after cued and delivered punishment. Interestingly, no circuit was associated with the adaptation to all rewarding outcomes; instead, dorsal striatal activation was exclusively associated with behavioral adaptation after cued and delivered reward. The results imply that partially distinct but somewhat overlapping circuits facilitate motor adjustment in response to different incentive outcomes.

These findings may have clinical implications for addiction and other disorders. Potential dysfunction in different circuits could explain particular difficulties in adjusting behavior in response to aversive outcomes of their drug-taking behavior. For instance, damage to the orbitofrontal cortex may especially impair punishment-induced behavioral adjustment. Furthermore, dysfunctions in different neural circuits might explain impairments of addicts in guiding their behavior according to nondrug rewards. Further research might disentangle the specific behavioral impairments induced by addiction as well as their neural correlates.

Acknowledgments

This study was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft; HE 2597/4-3) and by the Bernstein Center for Computational Neuroscience Berlin (BMBF grant 01GQ0411).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.04.001.

References

Abler, B., Walter, H., Erk, S., 2005. Neural correlates of frustration. NeuroReport 16, 669–672.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat. Neurosci. 2, 1032–1037.

Anderson, S.W., Barrash, J., Bechara, A., Tranel, D., 2006. Impairments of emotion and real-world complex behavior following childhood-or adult-onset damage to ventromedial prefrontal cortex. J. Int. Neuropsychol. Soc. 12, 224–235.

Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7 (4), 254–266.

Bartels, A., Zeki, S., 2004. The neural correlates of maternal and romantic love. NeuroImage 21, 1155–1166.

Baxter, M.G., Murray, E.A., 2002. The amygdala and reward. Nat. Rev., Neurosci. 3, 563–573.

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7–15.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S.W., Nathan, P.E., 2001. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia 39, 376–389.

Bermpohl, F., Pascual-Leone, A., Amedi, A., Merabet, L.B., Fregni, F., Gaab, N., Alsop, D., Schlaug, G., Northoff, G., 2006. Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. NeuroImage 30, 588–600.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Brain Res. Rev. 28, 309–369.

Breiter, H.C., Aharon, I., Kahneman, D., Dale, A., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30, 619–639.

Buechel, C., Dolan, R.J., 2000. Classical fear conditioning in functional neuroimaging. Curr. Opin. Neurobiol. 10, 219–223.

Cohen, M.S., 1997. Parametric analysis of fMRI data using linear systems methods. NeuroImage 6, 93–103.

Cohen, M.X., Ranganath, C., 2005. Behavioral and neural predictors of upcoming decisions. Cogn. Affect. Behav. Neurosci. 5, 117–126.

Cohen, M.X., Ranganath, C., 2007. Reinforcement learning signals predict future decisions. J. Neurosci. 27, 371–378.

Cools, R., Clark, L., Owen, A.M., Robbins, T.W., 2002. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. J. Neurosci. 22, 4563–4567.

Critchley, H.D., 2005. Neural mechanisms of autonomic, affective, and cognitive integration. J. Comp. Neurol. 493, 154–166.

Critchley, H.D., Mathias, C.J., Dolan, R.J., 2002. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron 33, 653–663.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

Critchley, H.D., Rotshtein, P., Nagai, Y., O'Doherty, J., Mathias, C.J., Dolan, R.J., 2005a. Activity in the human brain predicting differential heart rate responses to emotional facial expressions. NeuroImage 24, 751–762.

Critchley, H.D., Tang, J., Glaser, D., Butterworth, B., Dolan, R.J., 2005b. Anterior cingulate activity during error and autonomic response. NeuroImage 27, 885–895.

Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. J. Neurophysiol. 84, 3072–3077.

Delgado, M.R., Miller, M.M., Inati, S., Phelps, E.A., 2005. An fMRI study of reward-related probability learning. NeuroImage 24, 862–873.

Di Chiara, G., 2002. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav. Brain Res. 7, 75–114.

Duvernoy, H., 1999. The Human Brain. Surface, Blood Supply, and Three-Dimensional Sectional Anatomy, 2 ed. Springer-Verlag, Wien.

Eslinger, P.J., Damasio, A.R., 1985. Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35, 1731–1741.

Everitt, B.J., Wolf, M.E., 2002. Psychomotor stimulant addiction: a neural systems perspective. J. Neurosci. 22, 3312–3320.

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.

Frank, M.J., Woroch, B.S., Curran, T., 2005. Error-related negativity predicts reinforcement learning and conflict biases. Neuron 47, 495–501.

Gottfried, J.A., Dolan, R.J., 2004. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nat. Neurosci. 7, 1145–1153.

Gottfried, J.A., O'Doherty, J., Dolan, R.J., 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301, 1104–1107.

Haruno, M., Kuroda, T., Doya, K., Toyama, K., Kimura, M., Samejima, K., Imamizu, H., Kawato, M., 2004. A neural correlate of reward-based behavioral learning in caudate nucleus: a functional magnetic resonance imaging study of a stochastic decision task. J. Neurosci. 24, 1660–1665.

Holroyd, C.B., Coles, M.G., 2002. The neural basis of human error

processing: reinforcement learning, dopamine, and the error-related negativity. Psychol. Rev. 109, 679–709.
Juckel, G., Schlagenhauf, F., Koslowski, M., Wustenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage 29, 409–416.
Kim, H., Shimojo, S., O'Doherty, J.P., 2006. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. Public Libr. Sci. 4.
Knutson, B., Cooper, J.C., 2005. Functional magnetic resonance imaging of reward prediction. Curr. Opin. Neurol. 18, 411–417.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21, RC159.
Knutson, B., Fong, G.W., Bennett, S.M., Adams, C.M., Homme, D., 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. NeuroImage 18, 263–272.
Kringelbach, M.L., Rolls, E.T., 2003. Neural correlates of rapid reversal learning in a simple model of human social interaction. NeuroImage 20, 1371–1383.
Kuhnen, C.M., Knutson, B., 2005. The neural basis of financial risk taking. Neuron 47, 763–770.
Luu, P., Tucker, D.M., Derryberry, D., Reed, M., Poulsen, C., 2003. Electrophysiological responses to errors and feedback in the process of action regulation. Psychol. Sci. 14, 47–53.
Luu, P., Tucker, D.M., Makeig, S., 2004. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin. Neurophysiol. 115, 1821–1835.
Nicola, S.M., Yun, I.A., Wakabayashi, K.T., Fields, H.L., 2004. Firing of nucleus accumbens neurons during the consummatory phase of a discriminative stimulus task depends on previous reward predictive cues. J. Neurophysiol. 91, 1866–1882.
O'Doherty, J.P., Critchley, H., Deichmann, R., Dolan, R.J., 2003. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. J. Neurosci. 23, 7931–7939.
O'Doherty, J.P., Dayan, P., Schultz, J., Deichmann, R., Friston, K., Dolan, R.J., 2004. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304, 452–454.
Pagnoni, G., Zink, C.F., Montague, P.R., Berns, G.S., 2002. Activity in human ventral striatum locked to errors of reward prediction. Nat. Neurosci. 5, 97–98.
Panksepp, J., 1998. Affective Neuroscience. The Foundations of Human and Animal Emotions. Oxford University Press, New York.
Pessiglione, M., Seymour, B., Flandin, G., Dolan, R.J., Frith, C.D., 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 442, 1042–1045.
Pickens, C.L., Saddoris, M.P., Setlow, B., Gallagher, M., Holland, P.C., Schoenbaum, G., 2003. Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. J. Neurosci. 23, 11078–11084.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.
Skinner, B., 1953. Science and Human Behavior. Free Press, New York.
Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, New York.
Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D.F., Buchel, C., 2006. Dissociable systems for gain-and loss-related value predictions and errors of prediction in the human brain. J. Neurosci. 26, 9530–9537.