

# Orbital Prefrontal Cortex and Guidance of Instrumental Behavior of Rats by Visuospatial Stimuli Predicting Reward Magnitude

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The orbital prefrontal cortex (OPFC) is part of a circuitry mediating the perception of reward and the initiation of adaptive behavioral responses. We investigated whether the OPFC is involved in guidance of the speed of instrumental behavior by visuospatial stimuli predictive of different reward magnitudes. Unoperated rats, sham-lesioned rats, and rats with bilateral lesions of the OPFC by N-methyl-D-aspartate (NMDA) were trained in a visuospatial discrimination task. The task required a lever press on the illuminated lever of two available to obtain a food reward. Different reward magnitudes were permanently assigned to lever presses to respective sides of the operant chamber; that is, responses to one lever (e.g., the left one) were always rewarded with one pellet and responses to the other lever with five pellets. On each trial, the position of the illuminated lever was pseudorandomly determined in advance. Results revealed that OPFC lesions did not impair acquisition of the task, as the speed of conditioned responses was significantly shorter with expectancy of a high reward magnitude. In addition, during reversal, shift and reshift of lever position–reward magnitude contingencies and under extinction conditions, performance of the OPFC-lesioned and control groups did not differ. It is concluded that the OPFC in rats might not be critical for adapting behavioral responses to changes of stimulus–reward magnitude contingencies signaled by visuospatial cues.

The orbital prefrontal cortex (OPFC) might be part of a circuitry through which information on the motivational significance of stimuli mediates the selection and execution of reward-directed behavioral responses (Schoenbaum and Setlow 2001; Cardinal et al. 2002). This hypothesis is based on findings in rats and primates that the acquired motivational value of cues is encoded in OPFC (Lipton et al. 1999; Rogers et al. 1999; Yonemori et al. 2000; Schroeder et al. 2001). Electrophysiological data further indicate that neuronal activity in OPFC represents the conjunction of the acquired incentive value of the cues with the use of that information to guide behavior (Schoenbaum and Eichenbaum 1995; Schoenbaum et al. 1999). Furthermore, cue-selective firing in OPFC is altered markedly when cues associated with reinforcers are changed (Thorpe et al. 1983; Schoenbaum et al. 1999, 2000). In line with these results, primates, including humans, with OPFC lesions exhibit impairments after changes of stimulus–reward contingencies (Meunier et al. 1997; Elliott et al. 2000).

At present, however, there are only few studies investigating the role of the OPFC in rats in control of behavior. OPFC-lesioned rats are mildly impaired at acquiring new reinforcement contingencies in a continuous delayed-nonmatching-to-sample task (Otto and Eichenbaum 1992), but

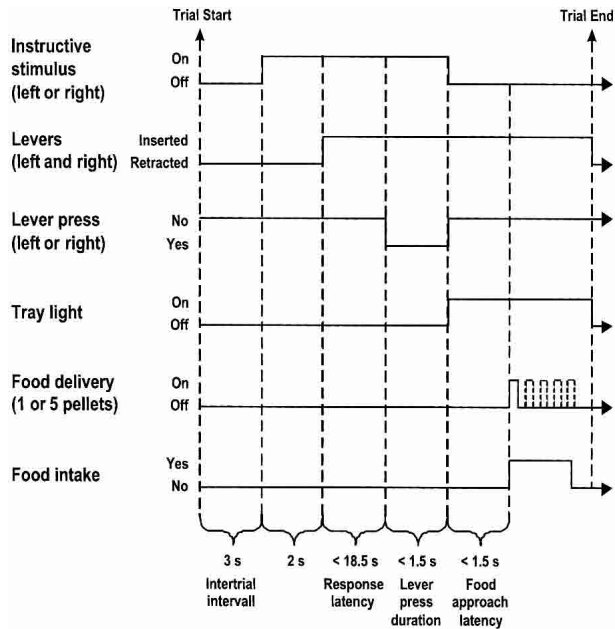
not in a go, no-go discrimination task (Schoenbaum et al. 2002). Furthermore, OPFC lesions in rats did not impair reversal learning in a Y-maze spatial alternation task (Eichenbaum et al. 1983) and a cheeseboard task (Corwin et al. 1994), but did so partially in olfactory discrimination tasks (Ferry et al. 2000; Schoenbaum et al. 2002). Besides, OPFC lesions in rats were found to impair conditioned responding after reinforcer devaluation (Gallagher et al. 1999) and performance in a T-maze task under extinction conditions (De Bruin 1994). Overall, the available data indicate that behavioral deficits after inactivation of the rat OPFC are subtle, strongly task-dependent, and in part inconsistent across different studies.

The present study sought to determine behavioral effects of OPFC lesions in more detail using a visuospatial discrimination task sensitive to subtle impairments in conditioned responses to visuospatial stimuli predictive of different reward magnitudes (Fig. 1). The task required a response to the illuminated of the two levers available to obtain a reward. Different reward magnitudes were permanently assigned to lever presses to respective sides of the operant chamber; that is, responses to one lever (for example, the left one) were always rewarded with one pellet and responses to the other lever with five pellets. On each trial, the position of the illuminated lever was pseudorandomly determined in advance. The purpose of this study was to analyze (1) whether OPFC-lesioned rats are able to acquire lever position–reward magnitude associations, and

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**Figure 1** Schematic representation of the order of trial events. The task demands responding to the illuminated of two levers (*left or right*) to obtain a reward. In the standard test procedure, one lever was associated with a high reward magnitude (five pellets, delivered at 0.2-sec intervals), and the other lever with a low reward magnitude (one pellet). On each trial, the position of the illuminated lever was randomly determined in advance. Accordingly, the instructive stimulus light was turned on at the beginning of each trial 2 sec before lever insertion and remained present until reward delivery. The rat had to respond to the illuminated lever within 18.5 sec with lever press durations shorter than 1.5 sec and to approach the food receptacle within 1.5 sec to obtain a reward. Responses on the illuminated lever that did not fulfill these criteria and responses on the not illuminated lever were not rewarded.

(2) whether OPFC-lesioned rats are able to adapt instrumental behavior to serial changes of lever position–reward magnitude contingencies. Preliminary findings of this work have previously been presented in abstract form (Bohn et al. 2001).

## RESULTS

### Histological Results

Infusion of NMDA resulted in extensive neuronal loss and gliosis in the lateral orbital and agranular insular regions. On average, lesions encompassed 80% of OPFC bilaterally, ranging from 60% to 100%. Lesion zones were defined by complete cell loss. Only rats were included in the OPFC-lesion group with lesions encompassing at least 60% of lateral orbital and agranular insular regions. Three rats with OPFC lesions did not reach this criterion and were excluded from the OPFC-lesion group. The largest lesions included moderate damage to the claustrum and ventrolateral orbital and to the frontal and parietal cortex. No relationship between any behavioral measure and the extent of the encroachment of

the lesions on adjacent structures was observed. Therefore, no animal was excluded from analysis because of large lesions including moderate damage to other areas. The approximate extent and placement of OPFC lesions of all included rats are presented in Figure 2. No mechanical damage in the OPFC because of the four injections per hemisphere was detected in sham-lesioned rats. Final sample sizes of treatment groups were  $n = 9$  (OPFC-lesioned group),  $n = 12$  (sham-lesioned group), and  $n = 12$  (unoperated group).

### Performance in Acquisition Sessions

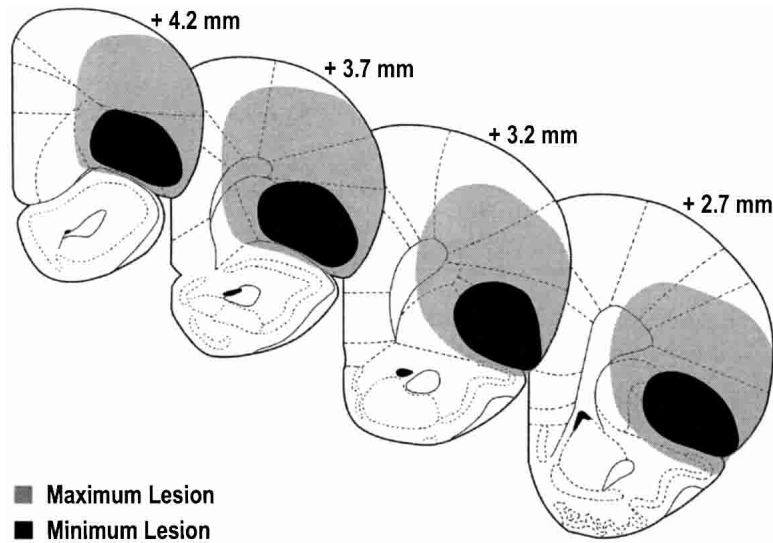
During acquisition, rats were trained in the standard test procedure of the visuospatial discrimination task demanding responses to the illuminated of two levers available to obtain a reward. Different reward magnitudes were permanently assigned to lever presses to respective sides of the operant chamber; that is, responses to one lever (e.g., the left one) were rewarded with one pellet and responses to the other lever with five pellets.

### Accuracy of Performance

The rate of correct responses to the lever associated with high reward magnitude increased mainly as a result of the decrease of false responses, that is, responses to the unlit lever, and reached  $96.8 \pm 1.0\%$  (OPFC-lesioned group),  $97.1 \pm 0.9\%$  (sham-lesioned group), and  $97.7 \pm 0.7\%$  (unoperated group) in the last acquisition session (Fig. 3A). The rate of correct responses to the lever associated with low reward magnitude did not increase and reached  $54.9 \pm 5.3\%$  (OPFC-lesioned group),  $57.1 \pm 5.7\%$  (sham-lesioned group), and  $52.7 \pm 6.3\%$  (unoperated group) in the last acquisition session (Fig. 3B), as the rate of false responses remained constant when the lever associated with low reward was illuminated. A three-way analysis of variance (ANOVA) on correct response rates with treatment groups and reward magnitudes as between factors and sessions as the within (repeated measures) factor indicated no significant differences between treatment groups, but indicated significant differences between reward magnitudes ( $F_{(1,60)} = 207.31$ ;  $P = 0.000^*$ ), sessions ( $F_{(5,300)} = 22.59$ ;  $P = 0.000^*$ ), and a significant reward magnitude  $\times$  session interaction ( $F_{(5,300)} = 31.51$ ;  $P = 0.000^*$ ). In addition, three-way ANOVAs on false, slow, and omitted response rates revealed no significant differences between OPFC-lesioned and control groups.

### Lever Press Duration Performance

As depicted in Figure 4, lever press durations (LPDs) of responses associated with high reward magnitude became significantly shorter than LPDs of responses associated with low reward magnitude, resulting in a significantly positive mean LPDs difference ( $\pm$ standard error of the mean [SEM]) of  $241 \pm 36$  msec (OPFC-lesioned group),  $182 \pm 34$  msec (sham-lesioned group), and  $191 \pm 54$  msec (unoperated



**Figure 2** Schematics showing the area of orbital prefrontal cortex damage. The approximate extent and placement of the orbital prefrontal cortex lesions for all rats used for data analysis are shown. The black and shaded regions, respectively, represent the minimum and maximum extent of cell loss across rats. Plates are adaptations from the atlas of Paxinos and Watson (1986). Numbers beside each plate correspond to millimeters anterior to bregma.

group) in the last acquisition session (main effect of reward magnitude:  $F_{(1,60)} = 16.40$ ;  $P = 0.0001$ ; main effect of sessions:  $F_{(5,300)} = 16.13$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 12.80$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### Response Latency Performance

Response latencies (RLs) of responses associated with high reward magnitude became significantly shorter than RLs of responses associated with low reward magnitude, resulting in a significantly positive mean RLs difference (main effect of reward magnitude:  $F_{(1,60)} = 55.44$ ;  $P = 0.000^*$ ; main effect of sessions:  $F_{(5,300)} = 55.98$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 4.08$ ;  $P = 0.0013$ ). RLs of the OPFC-lesioned rats did not differ significantly from those of sham-lesioned or unoperated rats.

#### Food Approach Latency Performance

Food approach latencies (FALs) of responses associated with high reward magnitude became significantly shorter than FALs of responses associated with low reward magnitude, resulting in a significantly positive mean FALs difference (main effect of reward magnitude:  $F_{(1,60)} = 9.28$ ;  $P = 0.0034$ ; main effect of sessions:  $F_{(5,300)} = 54.05$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 6.92$ ;  $P = 0.000^*$ ). FALs of the OPFC-lesioned rats did not differ significantly from those of sham-lesioned or unoperated rats.

#### Performance in Reversal Sessions

During reversal, lever position–reward magnitude contingencies valid during acquisition were reversed.

#### Accuracy of Performance

In the first reversal session, correct response rates to both levers were similar. During the following five sessions, the correct response rate to the lever associated with high reward magnitude increased (Fig. 3B) and, in turn, the false response rate decreased. The correct response rate to the lever associated with low reward magnitude decreased (Fig. 3A) and the false response rate increased in turn. A three-way ANOVA on correct response rates revealed significant differences between reward magnitudes ( $F_{(1,60)} = 80.59$ ;  $P = 0.000^*$ ) and a significant reward magnitude  $\times$  session interaction ( $F_{(5,300)} = 16.80$ ;  $P = 0.000^*$ ), but no significant differences between OPFC-lesioned, sham-lesioned and un-

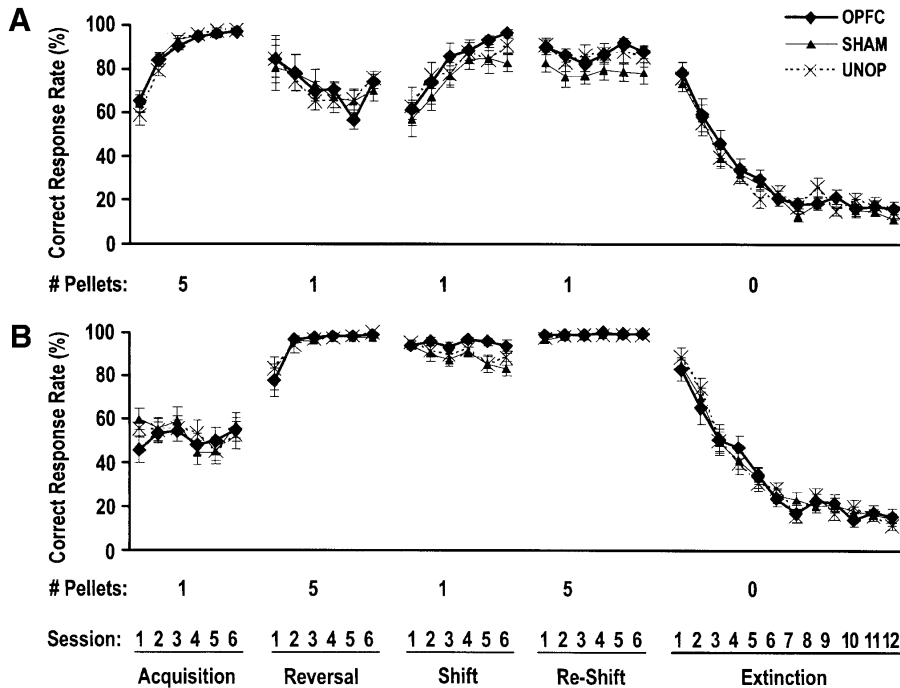
operated rats. Furthermore, three-way ANOVAs on false, slow, and omitted response rates revealed no significant differences between OPFC-lesioned, sham-lesioned, and unoperated rats either. In general, the accuracy of task performance of all treatment groups did not reach the same level as for the initial acquisition phase.

#### LPDs Performance

In the first reversal session, LPDs of responses were shorter to the lever associated with low reward magnitude (low reward magnitude: OPFC-lesioned group  $353 \pm 47$  msec, sham-lesioned group  $308 \pm 25$  msec, and unoperated group  $271 \pm 19$  msec; high reward magnitude: OPFC-lesioned group  $277 \pm 43$  msec, sham-lesioned group  $264 \pm 32$  msec, and unoperated group  $237 \pm 42$  msec). During the following five sessions, LPDs of responses associated with low reward magnitude became significantly longer than LPDs of responses associated with high reward magnitude, resulting in a significantly positive mean LPDs difference ( $\pm$ SEM) of  $130 \pm 36$  msec (OPFC-lesioned group),  $162 \pm 58$  msec (sham-lesioned group), and  $81 \pm 23$  msec (unoperated group) in the last reversal session (main effect of reward magnitude:  $F_{(1,60)} = 9.71$ ;  $P = 0.0028$ ; main effect of sessions:  $F_{(5,300)} = 2.90$ ;  $P = 0.0141$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 21.40$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats (Fig. 4).

#### RLs Performance

RLs of responses associated with high reward magnitude became significantly shorter than RLs of responses associ-



**Figure 3** Correct response rates for lever 1 (A) and for lever 2 (B). The number of pellets obtained after responding to lever 1 and 2 during acquisition, reversal, shift, reshift, and extinction sessions are depicted below each diagram. There were no significant differences between the three treatment groups (ANOVAs followed by the least square differences (LSD) post hoc test;  $P < 0.05$ ). (OPFC) Orbital prefrontal cortex-lesion group; (SHAM) sham-lesion group; (UNOP) unoperated group.

ated with low reward magnitude, resulting in a significantly positive mean RLs difference (main effect of reward magnitude:  $F_{(1,60)} = 63.60$ ;  $P = 0.000^*$ ; main effect of sessions:  $F_{(5,300)} = 4.75$ ;  $P = 0.0003$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 13.79$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### FALs Performance

FALs of responses associated with high reward magnitude became significantly shorter than FALs of responses associated with low reward magnitude, resulting in a positive mean FALs difference (main effect of sessions:  $F_{(5,300)} = 2.62$ ;  $P = 0.0244$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 16.71$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### Performance in Shift Sessions

In “shift” sessions, lever position–reward magnitude contingencies valid during reversal were changed. Presses on the lever associated with high reward during reversal were associated with low reward (termed here as “shift”); that is, after a correct response the rat received one instead of five

food pellets under the preceding reversal conditions. Thus, both levers were associated with low reward magnitude.

#### Accuracy of Performance

The correct response rate to the shifted lever (rewarded with one instead of five pellets under the preceding reversal conditions) decreased slightly (Fig. 3B) and the false response rate increased slightly, whereas the correct response rate to the other lever (rewarded with one pellet as under the preceding reversal conditions) increased markedly (Fig. 3A) and the false response rate decreased. A three-way ANOVA on correct response rates revealed significant differences between reward magnitudes ( $F_{(1,60)} = 16.82$ ;  $P = 0.0001$ ), sessions ( $F_{(5,300)} = 15.10$ ;  $P = 0.000^*$ ) and a significant reward magnitude  $\times$  session interaction ( $F_{(5,300)} = 28.35$ ;  $P = 0.000^*$ ) but no significant differences between OPFC-lesioned, sham-lesioned, and unoperated rats. Three-way ANOVAs on false,

slow, and omitted response rates revealed no significant differences between OPFC-lesioned, sham-lesioned, and unoperated rats either.

#### LPDs Performance

LPDs of responses to both levers did not differ significantly in shift sessions (main effect of sessions:  $F_{(5,300)} = 4.53$ ;  $P = 0.0005$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats (Fig. 4).

#### RLs Performance

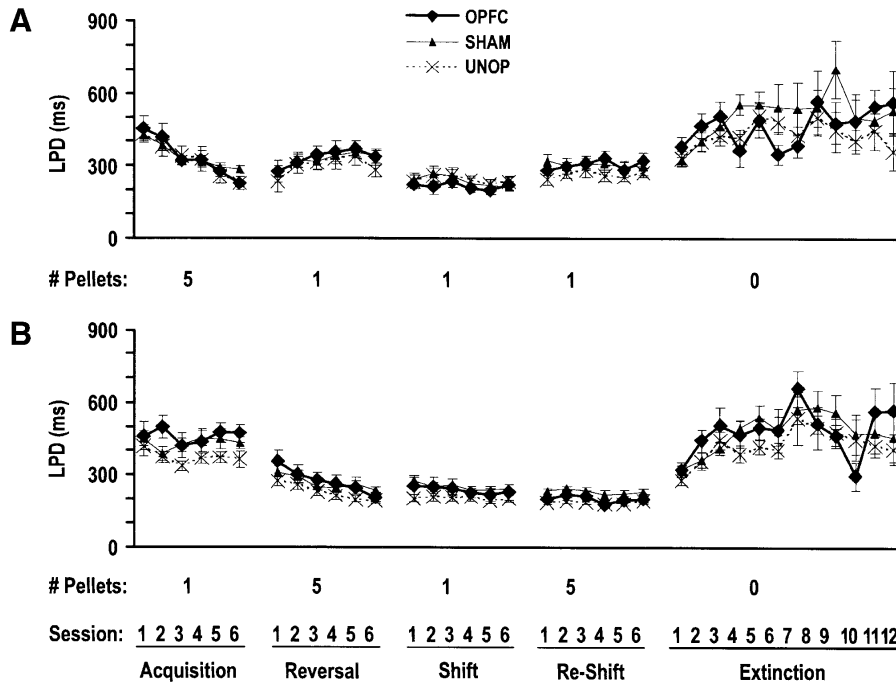
RLs of responses associated with the unshifted lever became significantly shorter (main effect of reward magnitude:  $F_{(1,60)} = 6.75$ ;  $P = 0.0118$ ; main effect of sessions:  $F_{(5,300)} = 2.81$ ;  $P = 0.0170$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### FALs Performance

FALs of responses to both levers did not differ significantly in shift sessions (main effect of sessions:  $F_{(5,300)} = 26.29$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### Performance in Reshift Sessions

In “reshift” sessions, lever position–reward magnitude contingencies valid during shift were changed. Presses on the



**Figure 4** Lever press durations (LPDs) for correct trials. (A) LPDs for lever 1. (B) LPDs for lever 2. The number of pellets obtained after responding to lever 1 and 2 during acquisition, reversal, shift, reshift, and extinction sessions are depicted below each diagram. There were no significant differences between the three treatment groups (ANOVAs followed by the LSD post hoc test;  $P < 0.05$ ). (OPFC) Orbital prefrontal cortex-lesion group; (SHAM) sham-lesion group; (UNOP) unoperated group.

lever associated with a down-shift from high to low reward magnitude during “shift” were associated with high reward again (termed here as “reshift”); that is, the test procedure was the same as during reversal with one lever associated with low reward magnitude and the other with high reward magnitude.

#### Accuracy of Performance

The rate of correct responses to the reshifted lever (rewarded with five pellets instead of one pellet under the preceding shift conditions) reached nearly 100% (Fig. 3B), whereas the rate of correct responses to the other lever (rewarded with one pellet as under the preceding shift conditions) became lower and reached nearly 85% (Fig. 3A) (main effect of reward magnitude:  $F_{(1,60)} = 42.66$ ;  $P = 0.000^*$ ; main effect of sessions:  $F_{(5,300)} = 3.08$ ;  $P = 0.0099$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 4.93$ ;  $P = 0.0002$ ). Moreover, three-way ANOVAs on correct, false, slow, and omitted response rates revealed no significant differences between OPFC-lesioned, sham-lesioned, and unoperated rats.

#### LPDs Performance

LPDs of responses to the reshifted lever were significantly shorter than those to the other lever, resulting in a significantly positive mean LPDs difference ( $\pm$ SEM) of  $122 \pm 35$

msec (OPFC-lesioned group),  $108 \pm 40$  msec (sham-lesioned group), and  $68 \pm 16$  msec (unoperated group) in the last reshift session (main effect of reward magnitude:  $F_{(1,60)} = 33.84$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats (Fig. 4).

#### RLs Performance

RLs of responses to the reshifted lever became significantly shorter than those to the other lever, resulting in a significantly positive mean RLs difference (main effect of reward magnitude:  $F_{(1,60)} = 56.94$ ;  $P = 0.000^*$ ; main effect of sessions:  $F_{(5,300)} = 25.92$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 6.18$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### FALs Performance

FALs of responses to the reshifted lever became significantly shorter than those to the other lever, re-

sulting in a significantly positive mean FALs difference (main effect of reward magnitude:  $F_{(1,60)} = 14.11$ ;  $P = 0.0004$ ; main effect of sessions:  $F_{(5,300)} = 16.95$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 2.67$ ;  $P = 0.0220$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### Performance in Extinction Sessions

During extinction, lever position–reward magnitude contingencies valid during reshift were changed; that is, both levers predicted nonreward. Each rat was tested for 15 min per day as the criterion of 60 correct responses per session were not reached any more under extinction conditions.

#### Accuracy of Performance

Three-way ANOVAs on correct, false, slow, and omitted response rates and on the total number of trials per session revealed no significant differences between OPFC-lesioned, sham-lesioned, and unoperated rats. Correct response rates (main effect of reward magnitude:  $F_{(1,60)} = 5.73$ ;  $P = 0.0199$ ; main effect of sessions:  $F_{(11,660)} = 267.35$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(11,660)} = 3.26$ ;  $P = 0.0002$ ) (Fig. 3) and false response rates (main effect of reward magnitude:  $F_{(1,60)} = 9.58$ ;  $P = 0.0029$ ; main effect of sessions:  $F_{(11,660)} = 9.27$ ;  $P = 0.000^*$ ; reward magnitude  $\times$

session interaction effect:  $F_{(11,660)} = 5.44$ ;  $P = 0.000^*$ ) to both levers became significantly lower. The decrease of correct and false response rates was due to the marked increase in omitted response rates to both levers (main effect of sessions:  $F_{(11,660)} = 305.64$ ;  $P = 0.000^*$ ). The mean omitted response rate ( $\pm$ SEM) was  $5.5 \pm 2.2\%$  (OPFC-lesioned group),  $2.2 \pm 0.8\%$  (sham-lesioned group), and  $2.3 \pm 0.7\%$  (unoperated group) in the first extinction session, and  $75.6 \pm 4.0\%$  (OPFC-lesioned group),  $76.3 \pm 3.0\%$  (sham-lesioned group), and  $79.6 \pm 2.0\%$  (unoperated group) in the last extinction session. The total number of trials per session decreased during extinction (main effect of sessions:  $F_{(11,330)} = 77.40$ ;  $P = 0.000^*$ ). The total number of trials ( $\pm$ SEM) was  $74 \pm 3$  (OPFC-lesioned group),  $76 \pm 2$  (sham-lesioned group), and  $76 \pm 5$  (unoperated group) in the first extinction session, and  $46 \pm 1$  (OPFC-lesioned group),  $47 \pm 1$  (sham-lesioned group), and  $46 \pm 1$  (unoperated group) in the last extinction session.

#### LPDs Performance

LPDs of responses to both levers became longer and did not differ significantly in extinction sessions (main effect of session:  $F_{(11,660)} = 5.48$ ;  $P < 0.001$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats (Fig. 4).

#### RLs Performance

RLs of responses to both levers became significantly longer in extinction sessions (main effect of reward magnitude:  $F_{(1,60)} = 12.25$ ;  $P = 0.0009$ ; main effect of sessions:  $F_{(5,300)} = 20.23$ ;  $P = 0.000^*$ ; reward magnitude  $\times$  session interaction effect:  $F_{(5,300)} = 1.85$ ;  $P = 0.0425$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

#### FALs Performance

FALs of responses to both levers became significantly longer and did not differ significantly in extinction sessions (main effect of sessions:  $F_{(5,300)} = 23.45$ ;  $P = 0.000^*$ ). OPFC-lesioned rats did not differ significantly from sham-lesioned or unoperated rats.

## DISCUSSION

The present study demonstrates that lesions of the OPFC did not impair discriminative guidance of instrumental responses by visuospatial stimuli predictive of different reward magnitudes. During reversal, shift, and reshift of lever position-reward magnitude contingencies and under extinction conditions, performance of OPFC-lesioned and control rats did not differ. Thus, the OPFC in the rat might not be involved in adapting behavioral responses to changes of stimulus-reward magnitude contingencies signaled by visuospatial cues.

## NMDA Lesions of the OPFC

Lesions were generally large and, on average, encompassed about 80% of the OPFC bilaterally. The extent and placement of lesions are comparable to NMDA lesions of OPFC reported by Gallagher et al (1999) and Schoenbaum et al. (2002) using the same concentration of NMDA and comparable injection placements. As rats received four injections of vehicle or NMDA per hemisphere during stereotaxic surgery, it might be that this multiple injection procedure caused mechanical damage in sham-lesioned animals, producing behavioral deficits on its own. Therefore, we included an unoperated group of animals as an additional control group. Results demonstrate that both control groups, that is, sham-lesioned and unoperated rats, did not differ in any variable measured. In addition, inspection of cresyl violet stained slices from sham-lesioned rats depicted no signs of mechanical damage in OPFC. Thus, behavioral impairments due to multiple injections per hemisphere could be ruled out.

## Discrimination Task

The visuospatial discrimination task used here demands fast responses to the illuminated of two levers available. All parameters analyzed, namely, RLs, LPDs, and FALs, were found to be guided by the anticipated reward magnitude; that is, latencies were shorter if high reward was anticipated. In addition, comparable alterations of these parameters were observed in all treatment groups after serial changes of stimulus-reward magnitude contingencies throughout the experiment groups. These findings indicate that these parameters are at least partially redundant. However, RLs and FALs show higher variability, probably because they are influenced by inevitable inconsistencies of body positions in relation to the lever or food receptacle (see also Robbins et al. 1993). Therefore, we focus on LPDs data, as this parameter is less influenced by postural factors. After acquisition, LPDs of responses associated with low reward magnitude were significantly longer than those associated with high reward magnitude. Apparently, predictive information provided by the position of the illuminated lever produced a reward magnitude expectancy accounting for the LPDs difference. The difference between LPDs of responses associated with low and high reward magnitudes was about +200 msec, which is three- to fourfold higher than those determined in a nine-hole box task (Brown and Bowman 1995) or lever release task (Hauber et al. 2000, 2001). Furthermore, with the task used here, subtle drug-induced changes of performance were detectable, for example, amphetamine-induced changes of accuracy and LPDs performance (I. Bohn, unpubl.). Thus, the present task might be sensitive to analyze effects of OPFC lesions on guidance of instrumental behavior by expectancy of different reward magnitudes.

### Effects of OPFC Lesion on Performance During Acquisition

OPFC-lesioned and control rats displayed similar increases in their correct response rates, indicating that OPFC-lesioned rats had no sensorimotor impairment interfering with task acquisition. After acquisition, the rate of correct responses to the lever associated with high reward magnitude reached nearly 100% in all treatment groups, whereas the rate of correct responses to the other lever was approximately 50%. In turn, the rate of false responses was nearly 0% to the lever associated with high reward magnitude, but ~50% to the lever associated with low reward magnitude. Thus, rats of all treatment groups developed a response bias to the lever associated with high reward.

LPDs performance of OPFC-lesioned rats was comparable to control rats, indicating that the rat OPFC seems not to be involved in learning reward magnitude associations between visuospatial cues and reward magnitudes. It is likely that responding of OPFC-lesioned and control rats involves stimulus–reward associations, and not response–reward associations, as RLs to the lit lever were a function of the anticipated reward magnitude, as indicated by the visuospatial stimulus.

The failure to detect effects of OPFC lesions on acquisition corroborates and extends previous findings showing that OPFC-inactivated rats are able to acquire a two-lever task (De Bruin et al. 2000). Likewise, OPFC lesions in rats do not impair learning egocentric and allocentric spatial tasks (Corwin et al. 1994); a spatial location task (Ragozzino and Kesner 1999); and a go, no-go discrimination task (Schoenbaum et al. 2002). Overall, these data indicate that OPFC lesions do not impair the rats' ability to acquire spatial discrimination tasks.

### Effects of OPFC Lesion on Performance After Serial Changes of Lever Position–Reward Magnitude Contingencies

During reversal, shift, and reshift of contingencies between visuospatial stimuli and associated reward magnitudes, OPFC-lesioned and control rats displayed similar changes in their correct response rates. Likewise, during extinction, rates of correct responses to both levers as well as the number of trials per session decreased, and rates of omitted responses to both levers increased in OPFC-lesioned and control rats to the same extent. Furthermore, after changes of contingencies between visuospatial stimuli and reward magnitudes, LPDs of OPFC-lesioned and control rats showed corresponding changes. Together, these data indicate that instrumental behavior of all treatment groups during reversal, shift, and reshift was strongly directed to the respective outcome and was not habitual: LPDs became faster to the lever associated with high reward magnitude during reversal, became indifferent if both levers were associated with the same reward magnitude during shift, and

became faster again to the lever associated with high reward magnitude during reshift. Interestingly, after reshift, LPDs for responses associated with one pellet became longer, indicating that the reinstatement of different stimulus–reward magnitude contingencies reduces LPDs of responses associated with one pellet. As already observed during acquisition, responding of OPFC-lesioned and control rats during shift, reshift, and extinction is likely to involve stimulus–reward associations, and not response–reward associations, as RLs to the lit lever were a function of the anticipated reward magnitude. Thus, the present data provide strong evidence that the OPFC in rats is not involved in adapting instrumental responding to changes of contingencies between visuospatial stimuli and reward magnitudes.

This finding seems to be at variance with previous studies showing that OPFC lesions impair the adaptation of behavior to changes of stimulus–reinforcement contingencies (Rolls et al. 1994; Rolls 1996; Gallagher et al. 1999; Elliott et al. 2000; Ferry et al. 2000; Schoenbaum et al. 2002). However, as discussed by Eichenbaum et al. (1983), and Ragozzino and Kesner (1999), it is likely that task differences might account for these deviating results, as some tasks are spatial, whereas other ones are nonspatial. For instance, lesions of medial prefrontal cortex cause performance deficits in spatial discrimination tasks (e.g., Kolb et al. 1974; Eichenbaum et al. 1983; Ragozzino and Kesner 1999), whereas lesions of OPFC do not impair learning of spatial reversals in a Grice box (Kolb et al. 1974), a cheeseboard (Corwin et al. 1994), and a Y-maze (Eichenbaum et al. 1983) task. On the other hand, there is consistent evidence that OPFC lesions impair performance in nonspatial tasks (Rolls et al. 1994; Rolls 1996; Gallagher et al. 1999; Elliott et al. 2000; Ferry et al. 2000; Schoenbaum et al. 2002). Furthermore, we found changes in reversal learning in rats with OPFC lesions in a nonspatial version of the task used here (I. Bohn, C. Gierler, and W. Hauber, in prep.). The failure to detect behavioral effects of OPFC lesions might be related to the fact that the task used here is visuospatial in nature with a visual stimulus signaling the rewarded one of two levers and the position of the lever signaling the upcoming reward magnitude. In general, the OPFC is thought to be critically involved in guiding instrumental behavior by the anticipated incentive value of the discriminative stimulus (for review, see Schoenbaum et al. 2002). However, the present study demonstrates that OPFC-lesioned rats are able to adapt instrumental behavior to serial changes in stimulus–reward magnitude contingencies with visuospatial stimuli predicting the reward magnitude. Thus, it seems to depend on the nature of the stimulus in terms of spatial versus nonspatial as to whether OPFC lesions do or do not impair the ability of rats to adjust their instrumental behavior appropriately.

The extinction data presented here further indicate

that instrumental behavior of control and OPFC-lesioned rats was guided by the outcome, as the accuracy of task performance decreased and LPDs of responses became significantly slower. In nonspatial tasks, however, OPFC inactivation led to a diminished response inhibition during extinction (Kolb et al. 1974; De Bruin et al. 2000). The failure to detect response disinhibition during extinction in the task used here might be related to the fact that guidance of instrumental behavior in visuospatial tasks does not rely on an intact OPFC.

### OPFC and a Visuospatial Discrimination Task

The OPFC is thought to be part of a circuitry through which information on the incentive value of stimuli mediates the selection and execution of reward-directed behavioral responses. In rats, the OPFC has been shown to be critically involved in adapting behavior to changing relationships between cues and outcomes (for review, see Schoenbaum et al. 2002 for review). To the best of our knowledge, the present data using a visuospatial discrimination task demonstrate for the first time that rats with OPFC lesions showed behavioral flexibility to serial changes of stimulus–outcome contingencies, that is, during reversal, shift, and reshift, as well as during extinction. In all tests, discriminative guidance of the speed of instrumental behavior by visuospatial stimuli predictive of different reward magnitudes was unimpaired in OPFC-lesioned rats. Thus, the OPFC in rats might not be critical for adapting instrumental responses to changes of stimulus–reward magnitude contingencies signaled by visuospatial cues.

## MATERIALS AND METHODS

Experiments were performed according to the current German Law on Animal Protection and were approved by the proper authorities in Stuttgart, Germany.

### Subjects

Thirty-six male Sprague-Dawley rats (Charles-River) were maintained in a temperature- and humidity-controlled room on a reversed 12-h light–12-h dark schedule (lights on 1900–0700 h) with testing in the dark phase. All rats were given ad libitum access to water. Standard laboratory maintenance chow (Altromin) was restricted to 12 g per animal and day. On days with behavioral tests, rats received in the testing apparatus a 6- to 10-g food reward (45-mg pellets, Bioserv). On these days, the amount of standard laboratory chow was adapted in order to keep body weights constant. Rats weighed 220–240 g on arrival and 230–260 g at the time of surgery.

### Surgery

For stereotaxic surgery, rats were anaesthetized with sodium pentobarbital (50 mg/kg, i.p.) (Sigma-Aldrich) following pretreatment with atropine sulphate (0.05 mg/kg, i.p.) (Sigma-Aldrich) and secured in a Kopf stereotaxic apparatus (Kopf Instruments). Standard stereotaxic methods were used for bilateral microinjections of N-methyl-D-aspartate (NMDA) (Tocris Cookson) at the following coordinates: 4.0 mm anterior to bregma, 2.2 mm lateral to midline and

4.6 mm ventral from skull surface, and 3.7 mm lateral to midline and 5.0 mm ventral from the skull surface. A second set of bilateral injections was made at 3.0 mm anterior to bregma, 3.2 and 4.2 mm lateral to midline, and 5.8 mm ventral from skull surface (Paxinos and Watson 1986). At each of the four sites per hemisphere, NMDA (20 mg/mL; OPFC-lesion group,  $n = 12$ ) or the Krebs'-Ringer's solution phosphate vehicle (sham-lesion group,  $n = 12$ ) was delivered in a volume of 0.1  $\mu$ L over a 2-min interval. The injector was left in situ for a further 6 min to allow for diffusion. During immediate postoperative recovery, rats of the lesion group were fed with a paste of water and pulverized standard laboratory maintenance chow. Each rat was given at least 2 wk to recover from surgery before postoperative training was started. One group of rats (unoperated group,  $n = 12$ ) did not undergo surgery. The lesion protocol was similar to the one described by Gallagher et al. (1999).

### Apparatus

Six operant test chambers (24 × 21 × 30 cm; Med Associates) were placed in separate sound-attenuating cubicles with fans providing a constant low level of background noise. Each chamber was supplied with two retractable levers, one on the left and the other on the right-hand side of one wall with an instructive stimulus light above each lever, and, in the middle of the opposite wall of the chamber, a food dispenser with a receptacle and an infrared photocell beam inside the receptacle. Experiments were controlled online (SmartControl-Interfaces; Med Associates) by a computer system (MedPC-Software; Med Associates).

### Visuospatial Discrimination Task

A visuospatial discrimination task similar to that described by Robbins et al. (1993) was used. Rats were trained in operant boxes requiring a response to the illuminated of two levers to obtain a reward. In the standard test procedure, responses to one of the levers (e.g., the left one) were permanently rewarded with five pellets (45-mg pellets, Bioserv), and responses to the other lever (e.g., the right one) were permanently rewarded with one pellet. Rats always consumed all of the pellets immediately prior to the beginning of the following trial. On each trial, the position of the illuminated lever was pseudorandomly determined in advance. Accordingly, the instructive stimulus light was turned on at the beginning of each trial 2 sec before lever insertion and remained present until reward delivery. To exclude side bias, for 50% of the rats, the left lever was associated with the high reward magnitude and the right lever was associated with the low reward magnitude. For the other 50% of the rats, the opposite pattern was used.

The following parameters were analyzed: RLs defined as latency from lever insertion until lever press, LPDs defined as latency from lever press until lever release, and FALs defined as latency from lever release until photocell beam disruption in the food receptacle (indicating onset of food intake) were recorded with an accuracy of 10 msec. For a correct trial, rats had to press the illuminated lever within 18.5 sec, to release the illuminated lever within 1.5 sec, and to approach the food receptacle within 1.5 sec. Responses with RLs >18.5 sec were defined as “omitted” responses, responses with LPDs >1.5 sec as “slow” responses, and responses on the not illuminated lever as “false” responses. Responses on the illuminated lever that did not fulfill these criteria and responses on the not illuminated lever were not rewarded. A daily individual session demanded 60 correct trials and lasted approximately 10 min. During the complete experimental period, all



rats were trained in one daily session on 5 d per week. A schematic representation of the order of trial events is given in Figure 1.

## Experimental Procedure

### Habituation

On the first day, subjects were habituated to the operant chamber. During this period, rats had access to food pellets being placed in the food receptacle. On the following days, a habituation program commenced with the levers inserted alternately. Pressing the inserted lever caused delivery of one pellet in the food receptacle. Rats continued this habituation program until a criterion of 20 responses on each lever was attained. Thereafter, rats were subjected to surgery.

### Acquisition Sessions

After 2 wk of recovery, rats were trained for six sessions in the visuospatial discrimination task. Thereafter, correct response rate was at least 60%; that is, rats needed at maximum 100 trials to attain the 60 necessary correct responses, and LPDs of responses associated with low reward magnitude were significantly longer than those associated with high reward magnitude.

### Reversal Sessions

After acquisition, reversal learning was tested for six sessions; that is, lever position–reward magnitude contingencies were reversed in the visuospatial discrimination task. After reversal sessions, the correct response rate was at least 60%, and LPDs of responses associated with low reward magnitude were significantly longer than those associated with high reward magnitude.

### Shift Sessions

After reversal, “shift” learning was tested for six sessions. The lever associated with a high reward magnitude during the preceding reversal sessions was “shifted”; that is, after a correct response, the rat received one instead of five food pellets under the preceding reversal conditions. Thus, both levers were associated with low reward magnitude.

### Reshift Sessions

After shift, “reshift” learning was tested for six sessions. The lever that had been shifted during the preceding shift sessions was “reshifted”; that is, after a correct response, the rat received five pellets instead of one pellet under the preceding shift conditions. After reshift sessions, the correct response rate was at least 60%, and LPDs of responses associated with low reward magnitude were significantly longer than those associated with high reward magnitude.

### Extinction Sessions

After reshift, extinction learning was tested for 12 sessions. Both levers predicted nonreward. Each rat was tested for 15 min per day as the number of omitted trials increased, and the number of correct trials per session decreased during extinction, and the 60 correct trials needed for a complete session were not reached any more.

## Data Analysis

Results revealed that rats had no side bias. They discriminated the lever positions associated with high or low reward regardless of whether the left or right lever in the operant test chamber was associated with high reward. Therefore, accuracy and RT data ob-

tained with both lever position–reward magnitude patterns were pooled for each treatment group.

Accuracy of task performance in a session was characterized by (1) the mean total number of trials ( $\pm$ SEM), (2) the percent means of correct responses to each lever ( $\pm$ SEM), (3) the percent means of omitted responses to each lever ( $\pm$ SEM), (4) the percent means of false responses to each lever ( $\pm$ SEM), and (5) the percent means of slow responses to each lever ( $\pm$ SEM). The last four parameters apply to the total number of responses to each lever. Three-way ANOVAs of each experimental period (acquisition, reversal, shift, reshift, extinction) were conducted with treatment groups and reward magnitudes as the between-subjects factors and sessions as the within-subjects (repeated measures) factor followed by LSD post hoc tests.

Discriminative guidance of instrumental behavior by the different reward magnitudes were analyzed using RLs, LPDs, and FALS data from correct responses, that is, responses to the illuminated lever within the time limits as described earlier. When averaging RLs, LPDs, and FALS data, a geometric mean was calculated for each rat for each session, because the geometric mean is less influenced by outlying data points than is the arithmetic mean. Overall means of RLs, LPDs, and FALS data represent the arithmetic average of the geometric means of individual rats (see Brasted et al. 1997).

Analysis of RLs, LPDs, and FALS data revealed corresponding changes in all treatment groups throughout the experiment; that is, when LPDs increased, RLs and FALS increased in a comparable manner; when LPDs remained constant, RLs and FALS remained constant as well; and when LPDs decreased, RLs and FALS decreased, too. Therefore, all three parameters measured in the present task seem to reflect the same neural processing underlying behavior. LPDs data were chosen for presentation in the figures, as RLs and FALS data are generally less sensitive than LPDs data: RLs and FALS data display a greater variability because of the inevitable inconsistencies in body positioning (Robbins et al. 1993).

After acquisition, LPDs of responses associated with low reward magnitude were significantly longer than those associated with high reward magnitude. A calculated “positive” difference between LPDs of responses associated with low versus high reward magnitude reflects intact guidance of responding by reward magnitude expectancy, as indicated by instructive stimuli (Hauber et al. 2000, 2001). LPDs data of each experimental period (acquisition, reversal, shift, reshift, extinction) were analyzed by three-way ANOVAs with treatment groups and reward magnitudes as the between-subjects factors and sessions as the within-subjects (repeated measures) factor followed by LSD post hoc tests.

Statistical computations were carried out with the STATISTICA ('99, StatSoft) statistical package. The level of statistical significance ( $\alpha$ -level) was set at  $P < 0.05$ .

## Histology

On completion of behavioral testing, rats were killed with Ethrane (Abbott) and transcardially perfused with 350 mL 0.02% heparin sodium salt solution (Gibco BRL), followed by 400 mL 4% formalin (Schuchardt). Brains were removed, postfixed in 4% formalin for 20 h, and stored in 30% glucose. Brain sections (30  $\mu$ m) were cut with a cryostat (Reichert and Jung), mounted on coated slides, and stained with cresyl violet. Sham lesions and OPFC lesions were analyzed with reference to the atlas of Paxinos and Watson (1986).

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