LESIONS OF THE PREFRONTAL CORTEX PRODUCE AN IMPAIRMENT IN
RATS' BEHAVIOUR ON A TIME-PLACE LEARNING TASK

by

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Abstract

This experiment examined the effect of medial prefrontal lesions on time-place learning in the rat. During the first phase, prior to lesioning, rats received training on an interval time-place task. Food was available on each of four levers for 3 consecutive minutes of a 12-min session. The levers provided food in the same sequence on all trials. Rats restricted the majority of their presses on each lever to the time in each session when it provided food and were able to anticipate when a lever was going to provide food.

During the second phase half the rats received lesions that were restricted to the medial prefrontal cortex. Following these very restricted lesions, rats were impaired in timing of the intervals. They tended to continue pressing a lever after it stopped providing food (i.e., perseverated, as if their internal clock was running slow). The third phase involved changing the order in which the levers provided food. Lesions had no discernable effect on the rats’ ability to learn the correct sequence of food availability. However, this change made the rats’ timing impairment even more noticeable.
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Lesions of the Prefrontal Cortex Produce an Impairment in Rats' Behaviour on a Time-Place Task

There is a growing body of literature suggesting that time-place behaviour is of fundamental biological importance in animals' foraging behaviour. Time-place information plays a role in a prominent theory of memory. Gallistel (1990) has posited that animals' memory may be organized on the basis of time-place information. This theory states that whenever a biologically significant event occurs, animals store a memory code consisting of the nature of the event, the time at which the event occurred, and the spatial location of the event. When animals later face a biological need, they consult their memory and determine where and when the need has been met in the past. They then use this information to guide their behaviour.

An early example of time-place based foraging behaviour was reported by Daan and Koene (1981). In this field study oystercatchers were observed engaging in foraging flights from their inland roosts to nearby tidal mudflats where they ate mussels. The timing of these flights was critical as there is only a narrow window of time in which the mussels are available. Despite the fact that the oystercatchers could not see the flats from their roosts, they flew to the mudflats just before the mussels were exposed by the low tide. Other field studies have observed similar behaviours in a tropical bee (Janzen, 1974), in kestrels (Rijnsdorp, Daan, & Dijkstra, 1981), and in scavenging birds, such as seagulls, crows, and pigeons (Wilkie, et al., 1996).

Similar behaviour has been reported in laboratory studies using garden warblers (Biebach, Gordijn, & Krebs, 1989; Biebach, Krebs, & Falk, 1994), ants (Harrison &
Breed, 1987; Schatz, Beugnon, & Lauchaud, 1994; Schatz, Lachaud, & Beugnon, 1999) pigeons (Saksida & Wilkie, 1994), golden shiners (Reebs, 1996), inanga fish (Reebs, 1999) and rats (Carr, Tan, & Wilkie, 1999). In one experiment investigating timing over periods of several minutes, Carr and Wilkie (1998) studied Long Evans rats in a square Plexiglas chamber containing a lever mounted on each of its four walls. Each lever provided food on a variable ratio (VR) schedule for a limited period of time. The first lever provided food for the first period in the session, the second lever provided food for the second period. Likewise in the third and fourth periods levers 3 and 4 provided food. The rats were able to learn which levers provided food at which times (i.e., they learned the sequence in which the levers provided food). In addition, the rats anticipated when a lever would provide food, as shown by their tendency to press the next rewarded lever in the sequence just before that lever began providing food. Previous studies have shown that rats do not time the entire session (i.e., from the beginning of the session to the end), but rather time the interval during which each lever provides food (i.e., start timing from the moment they receive the first pellet at a location and then reset the clock when they begin receiving pellets on another lever). It has been theorized that the interval is timed with a stop-watch like mechanism that resets at the end of each period (for a more complete discussion of possible timing mechanisms see Carr & Wilkie, 1998).

To date no information about the neural basis of rats’ time-place behaviour seems to exist. The main purpose of the present experiment was to begin to investigate this issue. Although several brain areas are likely involved in time-place behaviour, we chose to investigate the prefrontal cortex of the rat. We chose this area because time-place behaviour has an obvious planned, sequential organization to it.
There is ample evidence from humans, non-human primates, and rats that the prefrontal cortex is involved in processing information in order to guide behaviour over different points in time. Fuster (1980) posited that a primary function of the prefrontal cortex is to facilitate the temporal organization of behaviour, allowing an organism to utilize information that was obtained at one point in time in order to guide behaviour at a later point in time. Damage to the prefrontal cortex disrupts behaviours that require the execution of a planned sequence of events. Damasio (1979, 1994) found that human neuropsychological patients with focal damage in the prefrontal cortex had difficulty planning their daily work schedule in spite of otherwise largely preserved intellectual abilities. Similarly, in rats, damage to the medial prefrontal cortex disrupts behaviours such as food hoarding, which requires the animal to engage in a complex sequence of behaviours in order to store food efficiently (de Brabander, de Bruin, & van Eden, 1991). In addition, lesions to the prefrontal cortex also disrupt memory for order during a radial arm maze task (Kesner & Holbrook, 1987) As such, it is possible that the rat medial prefrontal cortex may also play a role in timing behaviour during time-place learning in an operant chamber, which requires a planned sequence of behavioural responses in order to receive food in an efficient manner.

In the present experiment rats were first trained on a time-place task in which each of four spatially distinct levers provided food for 3 min. Upon mastering this task experimental animals received lesions to the medial prefrontal cortex whereas control animals were anaesthetized but not operated on. The effect of damage to the medial prefrontal cortex on the execution of a previously acquired time-place task was then ascertained. In the final stage of the experiment the rats were required to learn a new
sequence of food availability on the four levers. The new sequence phase was included to determine whether damage to the medial prefrontal cortex impaired the acquisition of new time-place information.

Phase 1: Acquisition

Method

Subjects and Apparatus:

The subjects were seven experimentally naïve male Long Evans hooded rats acquired from Charles River (St. Constant, Quebec). At the beginning of the experiment they ranged in age from 100 to 167 days. The rats were maintained at approximately 90% of their free-feeding weight, adjusted for age. The rats received 45 mg Noyes A/I Pellets (P. J. Noyes Company, Inc., Lancaster, NH) during test sessions. At the end of test days and on non-test days rats received a standard rat diet (PMI Feeds, Inc., St. Louis, MO). Rats had free access to water except during test sessions.

Rats were housed individually in large opaque, plastic cages lined with either Carefresh (Absorption Corp., Bellingham, WA) or Bed o’ Cobs (Andersons, Maumee, OH) bedding. Each week rats were given paper products to build nests. The colony room was maintained on a 12 h light-dark cycle, with light onset at 0730 and offset at 1930. Rats received an average of two sessions per week of behavioural enrichment. Enrichment consisted of being placed in a chamber containing various tubes, ladders, and toys for 20 min. Throughout the duration of the experiment, the rats were maintained in strict accordance with Canadian Council on Animal Care (CCAC) guidelines.

Rats were tested in a transparent Plexiglas chamber (31 x 46 x 46 cm). The chamber was located on a bench (90 cm height) in a small, well lit room (157 x 206 x 273
cm). The floor of the chamber was covered with 2 cm of Bed o' Cobs (Andersons, Maumee, OH) bedding. Centered on each of the four walls, 4 cm from the floor was a lever. A brass food cup was located next to the lever. Lever presses were recorded by the closure of a microswitch mounted on each lever. Four pellet hoppers (Scientific Prototype Mfg. Corp., New York, NY, Model No. D700) were mounted on top of the chamber. When operated, the hoppers dispensed 45 mg Noyes A/I reward pellets into the food cups next to the levers. A small cue light (28 V DC) was mounted above each lever. A C++ program running on a nearby networked PC carried out data collection and equipment control.

Procedure:

Rats initially were exposed in groups of three or four to the testing chamber. During this exposure phase all four of the levers provided food reinforcement on a continuous reinforcement (CRF) schedule. Once all rats were consistently lever pressing they began individual training. During individual training rats were gradually shifted from the CRF schedule to a variable ratio (VR) 16 (i.e., on average every 16th response is reinforced).

When rats were consistently pressing on a VR 16 they began training on the time-place task. Rats received a single session 5 days per week. The order in which the rats were tested varied randomly across days. Sessions began between 1 and 5 hrs after colony light onset. Rats were placed into the testing chamber and a 2-min non-reinforcement period began. Responses had no consequences during this time. The purpose of this non-reinforcement period was to allow rats sufficient time to patrol and inspect the chamber and food sites before testing began. After this 2-min non-reinforced
period the cue lights came on and the session proper began. (For a more detailed
discussion of this non-reinforced period see Wilkie, Willson, & Carr, 1999.)

Test sessions were 12-min long and were divided into four equal length quarters. During each quarter only one lever provided reward pellets according to a VR 16. The four levers provided food in the same order for all rats in all sessions. The lever on the east wall provided reinforcement during the first quarter, the lever on the north wall provided reinforcement during the second quarter, and so on. The timing of each lever press and reward delivery was recorded to a 1-s accuracy on a remote server computer. A data file was generated in which the time at which each response occurred was recorded (time-stamp), in addition to which lever was pressed, and whether the response resulted in the delivery of a food pellet.

At the end of the 12-min session, rats were transported back to their home cages. Rats were fed at the end of the work day (approximately 1700) the remaining amount of their daily food ration to maintain them at approximately 90% of their body weight. Rats received 160 sessions during Phase 1.

Results and Discussion

Results are reported for the last 30 sessions of Phase 1. We computed each rat’s mean response rate on each of the four levers during each of the 24 30-s recording bins. Differences in overall response rates across the levers were removed by normalizing each rat’s mean response rate distribution for each lever. This normalization entailed expressing each rat’s mean response rate on a given lever during each bin as a percentage of the rat’s maximum response rate per bin on that lever. This yielded normalized mean response rates that ranged from 0 to 100.
An overall mean response rate distribution was then computed for each lever. This was accomplished by finding the average for each bin across animals. This was again normalized so that a maximum of 100 existed for each lever. These overall mean response rate distributions were broken down into two groups: One set for the animals that would receive lesions in Phase 2 and a second set for those animals that would not. This was done to verify that no differences existed between the groups before surgery. The normalized overall response rate distributions for each group for each of the 24 30-s bins are presented in Figure 1.

The results for the two groups of rats are very similar. Both groups of rats restricted the majority of their responding to the quarter in which the lever provided food. Furthermore, the rats began to press each lever prior to the start of the quarter when it would provide food, indicating that they were able to anticipate the onset of food availability on that lever. Responding reached its peak at approximately the middle of the reinforced quarter. Responding began to decrease just prior to the end of the quarter indicating that they anticipated the end of the quarter. This trend was consistent across all quarters.

There were no obvious differences in time-place behaviour between the control and the to-be-lesioned rats. Thus, both control and to-be-lesioned rats were able to time the interval and appeared to be able to learn the sequence that the levers provided food. In Phase 2 of the study, the effects of lesions to the medial prefrontal cortex on the performance of this time-place task was assessed.

Phase 2: Lesion
Method

Surgery: All rats were sedated with 7 mg/kg of xylazine and anaesthetized with 100 mg/kg of ketamine hydrochloride. In the 4 experimental rats bipolar insulated electrodes, which had only the tip exposed, were implanted into the prelimbic region of the medial prefrontal cortex at four co-ordinates (from bregma, and flat skull). The coordinates were: 1.) AP = +3.7 mm, ML ± 0.6 mm, DV = 3.5 mm and 2.) AP = +2.7 mm, ML ± 0.6 mm, DV = 3.8 mm. A 1.5 mA current was passed through the electrodes for 15 s.

Procedure: After surgery rats were given 4 weeks to recover. During these 4 weeks none of the rats received time-place training. Rats then received 64 sessions of the original time-place task. In addition, subjects also received 17 “open hopper tests” (OHT) sessions interspersed between the baseline sessions. During OHTs all levers provided food at all times during the 12-min sessions. The animal could press any lever throughout the entire OHT and continue to receive food on the VR 16 schedule. OHTs are administered to provide further evidence that the animals are in fact engaged in timing rather than some other strategy. One alternative strategy would be to discriminate when a lever is providing food and when it is not. This would be somewhat difficult (but not impossible) because the levers provided food on a VR 16. According to this strategy the rats could simply press one lever until it fails to give them food and then search for the next lever providing food. During OHTs it is usually the case that the animals switch to the next lever at approximately the correct time even though there are no contingencies in effect that necessitate them doing so. (For further discussion of OHTs see Carr, Tan, Thorpe, & Wilkie, 2001.)
Results

Data from the last 30 baseline sessions during this phase are presented in Figure 2. As can be seen both control and lesioned rats continued to restrict their responding on a particular lever to the quarter in which that lever provided reinforcement. One difference between the two groups appears to be the amount of perseveration (i.e., the percent of maximum response rate seems to remain higher after each quarter ends for the lesioned rats compared to control rats). This can be seen even more clearly in Figure 3, which shows the average normalized response rate collapsed across levers. This was accomplished by replotting the normalized response rate curves in Figure 2 around the six recording bins during which each lever provided food. The average response rate for each bin was then calculated by averaging across the four levers.

To investigate further this perseveration effect the mean percent of maximum response rate for each group was found for the three bins immediately following the end of the first three quarters (the last quarter perseveration could not be found since it was the end of the session). These were then averaged. A 3 (within bin) x 2 (between group) repeated measures analysis of variance was conducted. We examined these three bins because they are the three bins immediately following the end of the quarter when each lever no longer provided food. The rats' tendency to continue pressing a lever after it stopped providing food was taken as a measure of perseveration. The probability of the bin effect occurring solely by chance is very small ($F(2, 10) = 120.748, p < .001$). The probability that the group x bin interaction ($F(2, 10) = 1.045, p = .387$) and the group effect ($F(1, 5) = 2.923, p = .148$) arose solely by chance was larger.
The results for the 17 OHTs are shown in Figure 4. Although the rats do not appear to have restricted the majority of their responses to the quarter in which each lever usually provided food, their peak responding rate was during the appropriate quarter for each lever (with the exception of the lesion group during the third quarter). Perseveration was analyzed as for the baseline sessions. A 3 (within bin) x 2 (between group) repeated measures analysis of variance was again conducted. The probability that either the bin \( (F(2, 10) = 16.112, p = .001) \) or the bin x group \( (F(2, 10) = 4.789, p = .035) \) effects occurred solely by chance was small. It is much more likely that the group effect arose solely by chance \( (F(1, 5) = .010, p = .926) \). A t-test was conducted to determine whether the difference between the two groups on the first bin after the lever stopped providing food was likely to be due to chance. It was found that the probability of this difference occurring solely by chance was .160 \( (t(5) = 1.648) \).

Discussion

The results of Phase 2 of the present study revealed that lesions to the medial prefrontal cortex disrupted performance on this interval time-place task. This effect was most apparent in the OHTs. OHTs might be expected to be more sensitive to disruptions of internal timing mechanisms than baseline sessions. During baseline sessions it is possible for the rats to use the availability of food as a cue for when to switch levers. That is, on baseline sessions the lesioned rats may have known the correct sequence in which the levers provided food, and stayed on a lever until it stopped providing food, at which point they moved to the next lever in the sequence. In contrast, in the OHTs these cues are not available because all the levers provided food all the time. In the present study, rats with lesions to the medial prefrontal cortex continued to move from one lever to the
next in the correct sequence. The fact that the lesioned rats were still able to shift from lever to lever, rather than just staying on one lever for the entire session suggests that they were still timing, just not as accurately. It is as if their clock was running slow.

In Phase 3 the time intervals remained the same as in the previous two phases but the sequence in which the levers provided food was changed. This was done to assess whether the lesioned rats would be impaired on the acquisition of a new spatiotemporal sequence.

**Phase 3: Sequence Change**

**Method**

**Procedure:**

Rats were tested in the same fashion as they were in Phase 2 with one important exception. The order in which the levers provided food was changed. The levers were designated as follows in Phases 1 and 2: Lever 1 → Lever 2 → Lever 3 → Lever 4, but in Phase 3 they provided access to food as follows: Lever 3 → Lever 1 → Lever 4 → Lever 2. The rats received 44 sessions on this changed sequence condition.

**Results**

The percent correct on each lever during the correct quarter was found for each rat in blocks of three sessions. These percentages were then averaged for lesioned and control animals. These re-learning curves are shown in Figure 5. A repeated measures analysis of variance suggests that there are no major differences between the two groups in rate of acquisition (F(13, 65) = 0.468, p = .934). They also seem to reach the same level of asymptote.
Figure 6 shows the percent of maximum response rate for the four levers for the last 20 baseline sessions of this sequence change phase. This was calculated in the same manner as in the previous two phases. The lesioned rats again seemed to perseverate longer than the control animals. Figure 7 shows the average normalized response rate collapsed across levers. This was calculated in the same way as in Phase 2. Again we analyzed the perseveration effect by looking at the three bins immediately following the end of each quarter. A 3 (within bin) x 2 (between group) repeated measures analysis of variance was conducted. The probability that either the bin ($F(2, 10) = 521.979$, $p < .001$) or the bin x group ($F(2, 10) = 16.168$, $p = .001$) effect occurred solely by chance was small. The probability that the group effect ($F(1, 5) = 6.114$, $p = .056$) occurred solely by chance was larger. A t-test was conducted to determine whether the difference between the two groups on the first bin after the lever stopped providing food was likely to be due to chance. The probability of this difference occurring solely by chance was only .014 ($t(5) = 3.317$).

Discussion

In Phase 3 of the experiment, the rats with lesions of the medial prefrontal cortex did not exhibit an impaired ability to learn a new sequence (as demonstrated in the learning curves). It did however, result in their timing once again being less accurate – as if their clock were running slow. While the probability of the perseveration effects occurring in Phases 2 and 3 were slightly larger than .05 (that conventionally taken to be significant), the claim that there was in fact a real perseveration effect is strengthened by the fact that the probability of obtaining low p-values three times is itself quite small.

Histology:
Figure 8 shows the largest and smallest extent of the lesions for the four experimental rats. Histological assessment of the lesions revealed that the damage to the medial prefrontal cortex was centred primarily in the prelimbic and infralimbic regions, with one rat displaying slight damage to the more ventral regions of the anterior cingulate cortex.

General Discussion

Lesions to the medial prefrontal cortex produced a selective disruption during an interval time-place learning task. Both lesioned and control rats were able to perform the task, and switch from lever to lever. However, rats with lesions to the medial prefrontal cortex tended to perseverate during the course of a session, spending more time pressing a lever after a particular interval had expired. This deficit was even more pronounced to visual inspection in the open hopper test sessions and when the spatiotemporal sequence of food availability was changed.

In order to perform the time-place task optimally, animals must learn two different types of information. First, they must learn the sequence or order in which the different spatial locations (levers) are to be visited. They also have to learn how long to stay at each location. Contrary to our expectations medial prefrontal lesions had no discernable effect on the rats' ability to visit the different levers in a previously learned sequence. In addition, these lesions did not have any discernable effect on the rats' ability to learn a new sequence, as lesioned rats learned a new lever sequence at the same rate as the control rats. Thus, it appears that learning to switch from one location to another in order to receive food at preset intervals is a type of learning that does not require the integrity of the medial prefrontal cortex.
Lesions of the medial prefrontal cortex, on the other hand, did produce a selective impairment in the processing of temporal information. Lesioned rats were clearly capable of timing as indicated by the results of the OHTs. This alteration of behaviour was not a complete disruption of timing, since rats were still able to shift from one lever to the other, and did not simply start responding on a lever and continue pressing on that lever until the session ended. Instead, rats continued to move from one lever to the next, but were slower to shift from lever to lever relative to control rats. This finding suggests that an internal clock that rats consult to guide shifting behaviour from lever to lever was running slow, thereby causing them to overestimate temporal intervals. The trend to preseverate was also apparent on baseline sessions. It is likely that the rats were able to keep their timing error from accumulating by using the transition points as a cue for when their timing is off. That is, the lack of food at a lever when it was expected could be used to keep the amount of error in the system to a minimum. Likewise, it is also possible that the delivery of food on the lever next in the sequence is the factor that sets and restarts the internal clock. If true, then both groups’ internal clocks seem to be starting at similar points (see Figures 3 and 7). It is important to note that this does not imply that rats were not consulting an internal timing mechanism per se. Rather, it is more likely that rats tend to use both strategies during the interval time-place task; an internal timing strategy and external cues (i.e., transition points) to guide their behaviour. The fact that lesions of the medial prefrontal cortex resulted in rats spending longer periods pressing on a particular lever suggest that this brain region may be part of a neural circuit that facilitates timing guided by internal cues.
After the sequence in which the levers provided food was changed, the disruption in timing behaviour induced by prefrontal cortical lesions was even more apparent. Here, the perseveration was even noticeable on baseline sessions in which cues were available that indicated to the rats when they had not switched in time (i.e., they were no longer receiving food). Within 90 s after the end of a quarter the lesioned rats had almost completely stopped responding on the lever which previously provided food. Therefore, the transition points were still able to reduce the error in the system, but not to the same degree as prior to the sequence change.

Olton (1989) has also found that lesions to the prefrontal cortex caused impairments in timing. He trained rats to press a lever to obtain food on a fixed interval (FI) schedule. His FIs were much shorter than in the present experiment (10 and 20 s). He had probe trials in which food was not present interspersed between baseline sessions. He found that rats’ rate of responding increased just prior to when the rat normally obtained food. The point at which the rat’s peak rate of responding occurred was taken as a measure of when the rat expected food. Following this training some rats received lesions to the prefrontal cortex. These rats were then given additional baseline and probe trials. It was found that the lesioned rats’ peak was shifted to the right (compared to controls) indicating that they expected food at a time later than they usually received it. These results are very much in line with what was observed in the present study even though the time periods that we used were much longer. In fact, the similarity between Olton’s results and the present study is striking. Olton found that the lesioned rats in his study shifted their responding approximately 20%, and the lesioned rats in the present study shifted their responding approximately 17% (30/180 s). The probe trials used by Olton
(1989) were particularly revealing, since no external cues that indicated the end of the trial were provided; thus rats would need to rely on an internal timing mechanism to know when the trial had ended in a manner similar to the OHTs used in the present study. It is interesting to note that the lesions administered by Olton tended to be substantially larger than those administered in the present study. Olton (1989) utilized aspiration lesions, which damaged the anterior cingulate, premotor and prelimbic areas, whereas in the present study, damage was more restricted to the prelimbic cortex. Thus, it appears that the prelimbic cortex may be one region of the rat medial prefrontal cortex that is particularly important for timing.

Nonneman, Voigt, and Kolb (1974) have also found evidence for a role of the prefrontal cortex in timing. They showed that lesions of the medial prefrontal cortex resulted in disruptions in DRL (differential reinforcement of low response rate) performance. In the DRL paradigm rats are trained so that only responses made after a set amount of time since the last response are reinforced. This is further evidence of a timing impairment resulting from damage to the medial prefrontal cortex. As with the Olton paper, there were two major differences from the present experiment. First, Nonneman et al. (1974) used much shorter intervals (20 s) than were used in the present study. Second, they had much larger lesion areas. We were able to get noticeable impairments with very restricted lesions – in our case, lesions were limited to the prelimbic cortex.

In conclusion, the present data suggest that the medial prefrontal cortex of the rat plays a selective role during the performance of an interval time-place learning task, whereby it facilitates the use of internal timing mechanisms to guide behaviour during situations in which food is presented at different spatial locations at preset intervals. It
would be of interest for future studies on the neural substrates of timing to investigate the
neural regions that are involved in the sequencing aspect of the task and to ascertain the
importance of the prefrontal cortex in other aspects of timing such as time of day
discriminations (cf., Saksida & Wilkie, 1994).
References


Figure Captions

Figure 1. The normalized overall response rate distributions for the control (closed circles) and to-be-lesioned (open squares) rats on Levers 1, 2, 3 and 4 during baseline sessions for Phase 1. Responses on each lever were reinforced during the period bounded by the vertical dashed lines.

Figure 2. The normalized overall response rate distributions for the control (closed circles) and lesioned (open squares) rats on Levers 1, 2, 3 and 4 during baseline sessions for Phase 2. Responses on each lever were reinforced during the period bounded by the vertical dashed lines.

Figure 3. The normalized overall response rate distributions for the control (closed circles) and lesioned (open squares) rats collapsed across levers during baseline sessions for Phase 2. Responses on each lever were reinforced during the period bounded by the vertical dashed lines.

Figure 4. The normalized overall response rate distributions for the control (closed circles) and lesioned (open squares) rats on Levers 1, 2, 3 and 4 during open hopper test sessions for Phase 2. Vertical dashed lines represent the period in which the responses on the lever normally provide food.

Figure 5. Learning curves for acquisition of new sequence for control (closed circles) and lesioned (open squares) rats on Quarter 1, 2, 3 and 4. The percent correct is shown for blocks of 3 sessions.

Figure 6. The normalized overall response rate distributions for the control (closed circles) and lesioned (open squares) rats on Levers 1, 2, 3 and 4 during baseline
sessions for Phase 3. Responses on each lever were reinforced during the period bounded
by the vertical dashed lines.

**Figure 7.** The normalized overall response rate distributions for the control
(closed circles) and lesioned (open squares) rats collapsed across levers during baseline
sessions for Phase 3. Responses on each lever were reinforced during the period bounded
by the vertical dashed lines.

**Figure 8.** Histology. Schematic of coronal sections of the rat brain demonstrating
the smallest (grey shading) and largest (black shading) prefrontal cortex lesions induced
in the present study. Numbers beside each plate represent mm from bregma.
Figure 1

Percent of Maximum Response Rate

Lever 1

Lever 2

Lever 3

Lever 4

30 s Bin

Control

To-be-lesioned
Figure 2
Figure 3
Percent of Maximum Response Rate

Lever 1

Lever 2

Lever 3

Lever 4

Bin

Figure 4
Figure 5

Block

Percent Correct

Quarter 1 (Lever 3)

Quarter 2 (Lever 1)

Quarter 3 (Lever 4)

Quarter 4 (Lever 2)

--- Control

--- Lesion
Figure 6

Percent of Maximum Response Rate

Bin

Quarter 1 (Lever 3)

Quarter 2 (Lever 1)

Quarter 3 (Lever 4)

Quarter 4 (Lever 2)

--- Control

--- Lesion

Figure 6
Figure 7

Percent of Maximum Response Rate vs. Bin

- - Control
- - Lesion

FOOD