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Research report

Medial prefrontal cortex lesions impair decision-making on a rodent gambling task: Reversal by D1 receptor antagonist administration

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HIGHLIGHTS

- ► Lesions of the medial prefrontal cortex impaired stable decision-making.
- ► The D1 receptor antagonist SCH23390 reversed the lesion-induced decision-making deficit.
- ► The D2-like receptor antagonist haloperidol did not affect decision-making.

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ABSTRACT

Decision-making is a complex cognitive process that is impaired in a number of psychiatric disorders. In the laboratory, decision-making is frequently assessed using "gambling" tasks that are designed to simulate real-life decisions in terms of uncertainty, reward and punishment. Here, we investigate whether lesions of the medial prefrontal cortex (PFC) cause impairments in decision-making using a rodent gambling task (rGT). In this task, rats have to decide between 1 of 4 possible options: 2 options are considered "advantageous" and lead to greater net rewards (food pellets) than the other 2 "disadvantageous" options. Once rats attained stable levels of performance on the rGT they underwent sham or excitoxic lesions of the medial PFC and were allowed to recover for 1 week. Following recovery, rats were retrained for 5 days and then the effects of a dopamine D1-like receptor antagonist (SCH23390) or a D2-like receptor antagonist (haloperidol) on performance were assessed. Lesioned rats exhibited impaired decision-making: they made fewer advantageous choices and chose the most optimal choice less frequently than did sham-operated rats. Administration of SCH23390 (0.03 mg/kg), but not haloperidol (0.015–0.03 mg/kg) attenuated the lesion-induced decision-making deficit. These results indicate that the medial PFC is important for decision-making and that excessive signaling at D1 receptors may contribute to decision-making impairments.

1. Introduction

Decision-making is a complex cognitive process that involves assessing the risk, reward, and costs associated with different alternatives and then selecting that which will likely lead to the maximal benefit for the individual [1]. Decision-making deficits are commonly observed in a number of psychiatric conditions including attention-deficit hyperactivity disorder (ADHD [2]), substance abuse [3], Parkinson's disease [4–6], problem gambling [7,8] and schizophrenia [9–12]. These decision-making deficits can have devastating consequences and may contribute to the poor outcomes for afflicted individuals. Understanding the neural basis of optimal decision-making may allow us to develop strategies to treat decision-making impairments.

In the laboratory, decision-making is frequently tested using "gambling" tasks that are designed to simulate real-life decisions in terms of uncertainty, reward and punishment [1]. The Iowa Gambling Task (IGT; [13]), a task commonly used to assess decision-making in the laboratory, requires human subjects to choose between 4 different decks of cards. Unbeknownst to the subject, two of the decks of cards are associated with large financial gains, and unpredictable even larger losses such that continued choice of these decks leads to a net financial loss. The other two decks are associated with small financial gains, and unpredictable smaller losses such that continued choice of these decks leads to a net financial gain. Healthy control subjects develop a preference for the advantageous small win/small loss decks, while individuals with ventromedial PFC [13] or dorsolateral PFC [14] lesions fail to develop these preferences; instead they prefer the disadvantageous large reward/large loss decks.

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Recently, rodent "gambling" tasks have been developed that share many of the features of the human gambling tasks including uncertainty, reward and punishment [15,16]. The rodent gambling task (rGT) developed by Winstanley and colleagues [15,17] is notably similar to the IGT—there are 4 response options each of which is associated with a different reward/punishment contingency. Two of the response options are associated with small rewards (food pellets) and small, infrequent punishments (omission of reward and delay until the next trial). The other two options are associated with large rewards and large, frequent punishments. These response contingencies result in two options being relatively more "advantageous" than the other two "disadvantageous" options. Similar to healthy humans subjects, control rats develop a preference for the advantageous small reward/small punishment options over the disadvantageous large reward/large punishment options [15].

Using the rGT developed by Winstanley and co-workers [15,17], we aimed to determine whether lesions of the medial PFC negatively affected stable choice behavior. It has previously been observed that medial PFC and orbitofrontal cortex (OFC) lesions impair the development of an advantageous decision-making strategy in rats [17,18]. Once a stable strategy had been established however, OFC lesions did not affect choice behavior [17]. Given the role of the medial PFC in human decision-making [14] and because a number of psychiatric conditions display pathology in this brain area (e.g., [2–12] we aimed to determine whether medial PFC lesions would cause a change in rats' decision-making. Because "risk" based decision-making is modulated by dopamine [1,15,19] and because medial PFC lesions can cause changes in striatal dopamine transmission [20–22], we also investigated whether D1-like or D2-like receptor antagonist administration affected choice behavior in rats with sham or medial PFC lesions.

2. Materials and methods

2.1. Rats

Twenty-seven male Sprague-Dawley rats born at Oberlin College were used. Rats were maintained on a 14-h/10-h light–dark cycle (lights on at 0700 h) and were group housed until post-natal day (PND) 55; during this time they had unlimited access to food (Purina Rat Chow) and water. On PND 55 rats were pair housed until the time of surgery at which time they were housed singly. Upon pair housing and throughout the experiment rats were food restricted to ~85% of their free feeding weight; rats were fed after daily training sessions. Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals [23] and Oberlin College policies.

2.2. Drugs

Ibotenic acid and haloperidol were purchased from Sigma–Aldrich (St. Louis, MO). Ibotenic acid was dissolved in physiological saline (0.9%) to a final concentration of 10 μg/μl. Haloperidol was dissolved in 75% dimethyl sulfoxide to concentrations of 0.015 mg/ml and 0.03 mg/ml. SCH23390 was purchased from Tocris (Ellisville, MO) and was dissolved in saline (pH 6.5) to final concentrations of 0.03 mg/ml and 0.06 mg/ml.

2.3. Surgery

Rats were anesthetized with sodium pentobarbital (65 mg/kg, IP). The skull was exposed and burr holes drilled above the medial PFC. Rats received bilateral injections of either saline (n = 9) or ibotenic acid (n = 12) at the following coordinates (mm relative to bregma): AP + 2.8, ML ± 0.75, DV −3.3 and DV −2.3 [24]. Rats received two bilateral infusions, one at each DV coordinate. Each infusion delivered 0.4 μl/side of 10 μg/μl ibotenic acid or saline at a rate of 0.2 μl/min. The infuser remained in place for an additional 2 min following each infusion and then was raised for the second infusion or removed. Once the infuser was removed, the scalp was sutured shut.

2.4. Rodent gambling task (rGT)

The rGT was based upon that developed by Winstanely and co-workers [15,17]. Rats were trained and tested in 5-hole operant chambers enclosed in sound attenuating chambers (Med Associates, Vermont); the center hole was occluded throughout all experiments.

Table 1
Example of response contingencies across nose poke holes.

	Hole (H) 1	H2	H3	H4
# of rewards	4	1	3	2
Punishment duration (s)	40	5	30	10
Probability of punishment	0.6	0.1	0.5	0.2

Note: There were 4 different spatial arrangements of outcomes; one such arrangement is depicted here. An individual rat was assigned a single arrangement for the duration of the experiment. On rewarded trials the number of pellets indicated were delivered for that choice; on punished trials the no pellets were delivered.

Rats were first trained to retrieve food pellets (45-mg, Bio-Serv, Frenchtown NJ) from the food magazine over two consecutive days; during these sessions all holes were occluded. Next, rats were trained to nose poke in the holes under a continuous reinforcement schedule. In order to encourage equal nose poking in all 4 holes the two outer holes were occluded on the first session and the two inner holes occluded on the second session. On the third session and all subsequent sessions all 4 holes were open. The continuous reinforcement task began with the delivery of 1 food pellet and the illumination of the houselight and magazine light. Retrieval of the food pellet extinguished the magazine light and initiated a 5-s inter-trial interval (ITI). At the end of the ITI, lights at the rear of the holes (aperture lights) were illuminated and rats had 10 s to make a response in any hole. Responses resulted in the delivery of a food pellet reward (Bio-Serv). Rats were trained on the continuous reinforcement task until they received 100 rewards with less than 20 omissions in ~30 min.

Once rats reached criterion performance on the continuous reinforcement task they underwent 4 days of forced choice training on the full rGT. In each forced choice session only a single hole was available; this measure ensured that rats had experience with the contingencies associated with each hole prior to allowing rats to choose freely (see below). For the full rGT, sessions began with the delivery of a single food pellet and illumination of the houselight and the magazine light. Pellet retrieval extinguished the magazine light and initiated a 5-s ITI. At the end of the ITI the 4 aperture lights were illuminated and rats had 10 s (limited hold) to make a response in any hole. A response resulted in the assigned outcome (reward/punishment) for that hole (see Table 1 for example). On rewarded trials the aperture lights were all extinguished, the magazine light was illuminated and the appropriate number of pellets was delivered to the magazine. On punished trials no pellets were delivered and the houselight and all aperture lights, except the one from the chosen hole, were extinguished for the duration of the punishment period (i.e., the chosen hole remained illuminated throughout the punishment period). The next trial commenced at the end of the punishment period or once the rat retrieved the food pellet reward. Failing to respond within the limited hold was scored as an omission and responses occurring during the ITI were scored as premature responses. Omissions and premature responses were punished with a 5-s time out during which the houselight, magazine light and all aperture lights were extinguished. Each session lasted for a total of 60 min.

Four different spatial arrangements of the outcomes across holes were used. An individual rat however, was only trained and tested on a single spatial arrangement of outcomes. Two of the holes had relatively "advantageous" outcomes (increased total number of pellets over the entire 1 h session) due to the low probability (0.1–0.2) and short duration (5–10 s) of punishment periods (see Table 1). The advantageous choices were associated with smaller rewards (1–2 pellets). Two holes were associated with relatively "disadvantageous" outcomes due to the high probability (0.5–0.6) and long duration (30–40 s) of punishment. The disadvantageous choices were associated with larger rewards (3–4 pellets). The % responses at each hole and % advantageous responses ((#advantageous responses/total responses) × 100) were used as indicators of decision-making. Once % advantageous responding stabilized (<5% variability across days), rats underwent surgery and were allowed to recover for 5–7 days prior to beginning testing.

2.5. Testing

2.5.1. Effects of medial PFC Lesions on choice behavior

After a 5–7 day recovery period rats were retested on the rGT for 5 consecutive days in order to assess the effects of medial PFC lesions on decision-making.

2.5.2. Effects of SCH23390 on choice behavior

Next, the ability of the D1-like receptor antagonist SCH23390 to affect decision-making behavior in sham-operated and lesioned rats was assessed. SCH23390 (0.0, 0.03 and 0.06 mg/kg, IP) was administered 30 min prior to testing; doses were administered in a counterbalanced fashion. Rats were given at least 2 drug-free days between consecutive drug doses.

2.5.3. Effects of haloperidol on choice behavior

Finally, the ability of the D2-like receptor antagonist haloperidol to affect decision-making behavior in sham-operated and lesion rats was assessed. Haloperidol (0.0, 0.015 and 0.03 mg/kg, SC) was administered