Prefrontal Cortical Contribution to Risk-Based Decision Making

Damage to various regions of the prefrontal cortex (PFC) impairs decision making involving evaluations about risks and rewards. However, the specific contributions that different PFC subregions make to risk-based decision making are unclear. We investigated the effects of reversible inactivation of 4 subregions of the rat PFC (prelimbic medial PFC, orbitofrontal cortex [OFC], anterior cingulate, and insular cortex) on probabilistic (or risk) discounting. Rats were well trained to choose between either a “Small/Certain” lever that always delivered 1 food pellet, or another, “Large/Risky” lever, which delivered 4 pellets, but the probability of receiving reward decreased across 4 trial blocks (100%, 50%, 25%, and 12.5%). Infusions of gama-aminobutyric acid agonists muscimol/baclofen into the medial PFC increased risky choice. However, similar medial PFC inactivations decreased risky choice when the Large/Risky reward probability increased over a session. OFC inactivation increased response latencies in the latter trial blocks without affecting choice. Anterior cingulate or insular inactivations were without effect. The effects of prelimbic inactivations were not attributable to disruptions in response flexibility or judgments about the relative value of probabilistic rewards. Thus, the prelimbic, but not other PFC regions, plays a critical role in risk discounting, integrating information about changing reward probabilities to update value representations that facilitate efficient decision making.

Keywords: anterior cingulate, orbitofrontal cortex, prelimbic cortex, reversible inactivation, rat

Introduction

Decision making entailing cost–benefit evaluations about risks and rewards recruits numerous regions of the prefrontal cortex (PFC). Initial work by Damasio, Bechara, and colleagues, employing what is now referred to as the Iowa Gambling task, revealed that patients with damage to the ventromedial and orbital regions of the PFC make risky, disadvantageous choices compared with control subjects (Bechara et al. 1994, 1999; Damasio 1994). Subsequent research, using a variety of different tasks, patient populations, as well as neuroimaging in healthy subjects, has implicated multiple interconnected regions of the PFC in mediating these forms of decisions. These include the dorsolateral PFC (Ernst et al. 2002; Manes et al. 2002; Brand et al. 2004; Fellows and Farah 2005; Labudda et al. 2008), the medial and lateral regions of the orbitofrontal cortex (OFC; Rogers, Everitt, et al. 1999; Rogers, Owen, et al. 1999; Manes et al. 2002; Clark et al. 2003, 2008; Ernst et al. 2004; Fukui et al. 2005), the dorsal (Brodmann’s Area 24) and ventral (Area 32) regions of the anterior cingulate (Ernst et al. 2002; Labudda et al. 2008; Lawrence et al. 2009), and the insular cortex (Ernst et al. 2002; Bar-On et al. 2003; Clark et al. 2008; Smith et al. 2009).

Although multiple frontal lobe regions have been implicated in facilitating risk/reward decisions, the specific contribution that different PFC regions make to risk-based decision making remains unclear. For example, impaired decision making on the Iowa Gambling task displayed by patients with ventromedial PFC damage may reflect a failure to learn the win–lose contingencies associated with the different choice options, a preference for high-risk options regardless of potential loss or deficits in strategy acquisition and maintenance (Clark et al. 2004). Likewise, damage to either the OFC or dorsolateral PFC has been associated with impaired decision making in some studies (Bechara et al. 1994, 1999; Rogers, Owen, et al. 1999; Brand et al. 2004; Fellows and Farah 2005) but not in others (Bechara et al. 1998; Manes et al. 2002; Clark et al. 2003). Different regions of the anterior cingulate have been implicated in multiple aspects of decision making, depending on the type of task used. These include monitoring increasing potential or received gain (Rogers et al. 2004; Tom et al. 2007), loss or negative feedback (Blair et al. 2006; Marsh et al. 2007; Cohen et al. 2008), or changes in reward contingencies that require modifications in behavior (Bush et al. 2002; Cohen et al. 2008). These discrepant findings may be due in part to differences in the specific loci and laterality of damage that may vary considerably between subjects and may also encompass multiple PFC regions. Thus, studies that afford greater experimental control, as may be achieved with animal models, may help clarify how different PFC regions contribute to aspects of risk-based decision making.

One component of decision making that can be assessed in rodents is the evaluation of certain costs associated with different actions relative to the potential reward that may be obtained by those actions. In these studies, rats typically choose between smaller rewards associated with a nominal cost, and larger, yet more costly rewards (Floresco, St. Onge, et al. 2008). Dissociable regions of the rat PFC appear to mediate different forms of these cost–benefit judgments. The OFC appears to be a critical component of the circuitry underlying delay discounting, where animals choose between small, immediate rewards and larger, delayed rewards (Mobini et al. 2002; Winstanley et al. 2004; Rudebeck et al. 2006). On the other hand, the dorsal anterior cingulate has been implicated in mediating decisions related to effort costs associated with larger rewards (Walton et al. 2003; Rudebeck et al. 2006; Floresco and Ghods-Shariﬁ 2007).

Interestingly, there have been relatively few studies on the involvement of different regions of the rat PFC in risk-based decision making. Of these, the OFC has received the most

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attention. Mohini et al. (2002) reported that large lesions of the OFC (encompassing portions of the medial PFC) increased preference for a small, but certain, food reward relative to a larger reward delivered in a probabilistic manner. Another study used a procedure modeled after the Iowa Gambling task, where rats learned contingencies of decision alternatives in 1 session and adjusted choice based on evaluations of previous outcomes (Pais-Vieira et al. 2007). Rats with OFC lesions developed a preference for the high-risk/large reward (LR) over the low-risk/small reward (SR) option, even though the expected value of the 2 options was equal. In both of these studies, lesions were induced prior to training on the task, indicating that the OFC may play a role in the initial learning of risk/reward contingencies. In contrast, the contribution of the rat OFC to risk/reward judgments after animals have learned the relative value of different response options is unknown. Moreover, to our knowledge, there have been no studies on the contribution of the rodent medial PFC or insular cortex to risk-based decision making.

To address this issue, the present study investigated the effects of reversible inactivation of different subregions of the rat PFC on risk-based decision making, using a probabilistic discounting task conducted in an operant chamber. Rats chose between responses that yielded a small/certain food reward and a larger reward delivered in a probabilistic manner, where the odds of receiving the larger reward decreased over a session. Previous studies using similar procedures have implicated the nucleus accumbens (Cardinal and Howes 2005), the basolateral amygdala (Ghods-Sharifi et al. 2009), and the dopamine system (St Onge and Floresco 2009) in biasing choice toward larger, probabilistic rewards. Each of these systems shares connections with different regions of the PFC (Beckstead et al. 1979; McDonald 1991). In the present study, rats were well trained on this task prior to receiving reversible inactivations of 1 of 4 different PFC subregions. Each of these regions sends projections to the nucleus accumbens core (Brog et al. 1993), which has been shown previously to mediate to risk discounting (Cardinal and Howes 2005). Risk discounting was altered selectively by inactivation of the prelimbic region of the medial PFC, a region that is anatomically homologous to Area 32 of the human anterior cingulate (Uylings and van Eden 1990) but also shares functional homology to the dorsolateral PFC (Brown and Bowman 2002; Uylings et al. 2003). Accordingly, subsequent experiments were conducted to clarify the specific nature of the disruption in risk-based decision making induced by medial PFC inactivation.

**Experiment 1: The Effects of Inactivations of the Medial PFC, OFC, Anterior Cingulate, and Insular Cortex on Risk Discounting**

**Materials and Methods**

**Animals**

Male Long Evans rats (Charles River Laboratories, Montreal, Canada) weighing 275–300 g at the beginning of behavioral training were used for the experiment. On arrival, rats were given 1 week to acclimatize to the colony and food restricted to 85–90% of their free-feeding weight for an additional 1 week before behavioral training. Rats were given ad libitum access to water for the duration of the experiment. Feeding occurred in the rats’ home cages at the end of the experimental day, and body weights were monitored daily to ensure a steady weight loss during food restriction and maintenance or weight gain for the rest of the experiment. All testing was in accordance with the Canadian Council of Animal Care and the Animal Care Committee of the University of British Columbia.

**Apparatus**

Behavioral testing for all experiments described here was conducted in 12 operant chambers (30.5 × 24 × 21 cm; Med-Associates, St Albans, VT) enclosed in sound-attenuating boxes. The boxes were equipped with a fan to provide ventilation and to mask extraneous noise. Each chamber was fitted with 2 retractable levers, one located on each side of a central food receptacle where food reinforcement (45 mg; Bioserv, Frenchtown, NJ) was delivered via a pellet dispenser. The chambers were illuminated by a single 100-mA houselight located in the top center of the wall opposite the levers. Four infrared photobeams were mounted on the sides of each chamber. Locomotor activity was indexed by the number of photobeam breaks that occurred during a session. All experimental data were recorded by an IBM personal computer connected to the chambers via an interface.

**Lever-Pressing Training**

Our initial training protocols have been described previously (Floresco, Tse, et al. 2008; St Onge and Floresco 2009). On the day prior to their first exposure to the chambers, rats were given approximately 25 sugar reward pellets in their home cage. On the first day of training, 2–3 pellets were delivered into the food cup, and crushed pellets were placed on a lever before the animal was placed in the chamber. Rats were first trained under a fixed-ratio 1 schedule to a criterion of 60 presses in 30 min, first for one lever, and then repeated for the other lever (counterbalanced left/right between subjects). Rats were then trained on a simplified version of the full task. These 90 trial sessions began with the levers retracted and the operant chamber in darkness. Every 40 s, a trial was initiated with the illumination of the houselight and the insertion of 1 of the 2 levers into the chamber. If the rat failed to respond on the lever within 10 s, the lever was retracted, the chamber darkened, and the trial was scored as an omission. If the rat responded within 10 s, the lever retracted, and a single pellet was delivered with 50% probability. This procedure was used to familiarize the rats with the probabilistic nature of the full task. In every pair of trials, the left or right lever was presented once, and the order within the pair of trials was random. Rats were trained for approximately 5–6 days to a criterion of 80 or more successful trials (i.e., ≤10 omissions).

**Risk-Discounting Task**

The task was modified from Cardinal and Howes’ (2005) procedure, which we have previously used to assess the role of dopamine and the basolateral amygdala in risk-based decision making (Ghods-Sharifi et al. 2009; St Onge and Floresco 2009). Rats received daily sessions consisting of 72 trials, separated into 4 blocks of 18 trials. The entire session took 48 min to complete, and animals were trained 6–7 days per week. A session began in darkness with both levers retracted (the intertrial state). A trial began every 40 s with the illumination of the houselight and, 5 s later, insertion of one or both levers into the chamber (the format of a single trial is shown in Fig. 1). One lever was designated the Large/Risky lever, the other the
Small/Certain lever, which remained consistent throughout training (counterbalanced left/right). If the rat did not respond by pressing a lever within 10 s of lever presentation, the chamber was reset to the intertrial state until the next trial (omission). When a lever was chosen, both levers retracted. Choice of the Small/Certain lever always delivered one pellet with 100% probability; choice of the Large/Risky lever delivered 4 pellets but with a particular probability (see below). When food was delivered, the houselight remained on for another 4 s after a response was made, after which the chamber reverted to the intertrial state. Multiple pellets were delivered 0.5 s apart. The 4 blocks were comprised of 8 forced-choice trials where only one lever was presented (4 trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever press and the respective probability of receiving reinforcement over each block. This was followed by 10 free-choice trials, where both levers were presented and the animal chose either the Small/Certain or the Large/Risky lever. The probability of obtaining 4 pellets after pressing the Large/Risky lever varied across blocks: It was initially 100%, then 50%, 25%, and 12.5%, respectively, for each successive block. For each session and trial block, the probability of receiving the LR was drawn from a set probability distribution. Therefore, on any given day, the probabilities in each block may vary, but on average across many training days, the actual probability experienced by the rat will approximate the set value. Using these probabilities, selection of the Large/Risky lever would be advantageous in the first 2 blocks and disadvantageous in the last block, whereas rats could obtain an equivalent number of food pellets after responding on either lever during the 25% block. Therefore, in the last 3 trial blocks of this task, selection of the larger reward option carried with it an inherent “risk” of not obtaining any reward on a given trial. Latencies to initiate a choice and overall locomotor activity (photobeam breaks) were also recorded.

A priori we determined that if inactivation of a particular PFC region resulted in an increased preference for the Large/Risky lever, a separate group of animals would be trained on a similar discounting task, in which the probabilities associated with the Large/Risky lever increased, rather than decreased across the 4 blocks (i.e., 12.5%, 25%, 50%, and 100%). The purpose of this was to determine if an increased preference for the Large/Risky lever following PFC inactivation was due specifically to a general increase in risky choice or to alterations in other cognitive processes that facilitate risk discounting. All other aspects of the training procedures were identical to those described above.

Training Procedure, Surgery, and Microinfusion Protocol

Rats were trained on the task until as a group they 1) chose the Large/Risky lever during the first trial block (100% probability) on at least 80% of successful trials and 2) demonstrated stable baseline levels of choice. Brain inactivations were conducted once a group of rats displayed stable patterns of choice for 3 consecutive days, assessed using a procedure similar to that described by Winston et al. (2005), Floresco, Tsc, et al. (2008), and St Onge and Floresco (2009). In brief, data from 3 consecutive sessions were analyzed with a repeated-measures analysis of variance (ANOVA) with 2 within-subjects factors (Day and Trial Block). If the effect of Block was significant at the $P < 0.05$ level but there was no main effect of Day or Day × Trial Block interaction (at $P > 0.1$ level), animals were judged to have achieved stable baseline levels of choice behavior. After the stability criterion was achieved, rats were provided food ad libitum and 2 days later were subjected to surgery.

Rats were anesthetized with 100 mg/kg ketamine hydrochloride and 7 mg/kg xylazine and implanted with bilateral 23-gauge stainless steel guide cannulae into one of the following regions: the medial PFC (prelimbic cortex; anteroposterior [AP] = +3.4 mm; medial-lateral [ML] = ± 0.7 mm from bregma; and dorsoventral [DV] = −2.8 mm from dura); lateral OFC (AP = +3.9 mm; ML = ± 2.6 mm from bregma; DV = −2.9 mm from dura); anterior cingulate (AP = +2.0 mm; ML = ± 0.7 mm from bregma; and DV = −1.0 mm from dura); and agranular insular cortex (AP = +2.7 mm; ML = ± 3.8 mm from bregma; and DV = −3.8 mm from dura). For all surgical preparations, the mouthbar was set to −3.3 mm (flat skull). Thirty-gauge obdurators flush with the end of guide cannulae remained in place until the infusions were made. Rats were given at least 7 days to recover from surgery before testing. During this recovery period, animals were handled at least 5 min each day and food restricted to 85% of their free-feeding weight. Body weights were continued to be monitored daily to ensure a steady weight loss during this recovery period. Rats were subsequently retrained on the task for at least 5 days and until, as a group, they displayed stable levels of choice behavior. For 3 days before the first microinfusion test day, obdurators were removed, and a mock infusion procedure was conducted. Stainless steel injectors were placed in the guide cannulae for 2 min, but no infusion was administered. This procedure habituated rats to the routine of infusions in order to reduce stress on subsequent test days. The day after displaying stable discounting, the group received its first microinfusion test day.

A within-subjects design was used for all experiments. Inactivation of PFC regions was achieved by infusion of a drug.
solution containing the GABA<sub>A</sub> agonist muscimol (Sigma-Aldrich Canada, Oakville, Ontario, Canada) and the GABA<sub>B</sub> agonist baclofen (Sigma-Aldrich). Both drugs were dissolved separately in physiological saline at a concentration of 500 ng/µL and then combined in equal volumes, with the final concentration of each compound in solution being 250 ng/µL. Intracranial microinfusions used a volume of 0.5 µL so that the final dose of both baclofen and muscimol was 125 ng per side. These doses were chosen because we have found them to be effective at altering risk discounting when infused in other brain regions (Ghods-Shariﬁ et al. 2009). In addition, infusions of comparable doses of baclofen and muscimol in the OFC (Takahashi et al. 2009) or muscimol alone into the anterior cingulate (Ragozzino and Rozman 2007) have been reported to disrupt cognition. Note that these doses are substantially higher than doses used in previous experiments that have also reported behavioral effects (e.g., 10 ng; Corrigall et al. 2001). Infusions of gama-aminobutyric acid (GABA) agonists or saline were administered bilaterally into one of the PFC regions via 30-gauge injection cannulae that protruded 0.8 mm past the end of the guide cannulae, at a rate of 0.5 µL/75 s by a microsyringe pump. Injection cannulae were left in place for an additional 1 min to allow for diffusion. Each rat remained in its home cage for another 10-min period before behavioral testing. On the first infusion test day, half of the rats in each group received saline infusions and the other half received muscimol/baclofen. The next day, they received another training day with no infusion. If, for any individual rat, choice of the Large/Risky lever deviated by more than 15% from its preinfusion baseline, it received an additional day of training prior to the second infusion test. On the following day, rats received a second counterbalanced infusion of either saline or muscimol/baclofen.

**Histology**

After completion of all behavioral testing, rats were sacrificed in a carbon dioxide chamber. Brains were removed and fixed in a 4% formalin solution. The brains were frozen and sliced in 50-µm sections before being mounted and stained with Cresyl Violet. Placements were veriﬁed with reference to the neuroanatomical atlas of Paxinos and Watson (1998). The locations of acceptable infusions for rats used in Experiment 1 are presented in the right panels of Figure 2.

**Data Analysis**

The primary dependent measure of interest was the percentage of choices directed toward the Large/Risky lever for each block of free-choice trials factoring in trial omissions. For each block, this was calculated by dividing the number of choices of the Large/Risky lever by the total number of successful trials. The choice data were analyzed using 2-way within-subjects ANOVAs, with Treatment and Trial Block as the within-subjects factors. The main effect of block for the choice data was significant in all experiments ($P < 0.05$) indicating that rats discounted choice of the Large/Risky lever as the probability of the LR changed across the 4 blocks. This effect will not be mentioned further. Locomotor activity (photobeam breaks) and the number of trial omissions were analyzed with 1-way within-subjects ANOVAs. Response latencies were analyzed using either 2-way or 1-way within-subjects ANOVAs.

**Results**

**Medial PFC (Prelimbic)**

Initially, 16 rats were trained for this experiment. Two animals died during surgery, and the data from another rat was eliminated due to inaccurate placement. The remaining rats ($n = 13$) required an average of 35 days of training on the risk-discounting task prior to receiving counterbalanced infusions of saline or muscimol/baclofen into the medial PFC. Analysis of choice behavior following bilateral infusions of muscimol/baclofen or saline into the medial PFC revealed a significant main effect of treatment ($F(1,12) = 6.20, P < 0.05$; Fig. 2A, left panel). Medial PFC inactivation caused a significant increase in the proportion of choices directed toward the Large/Risky lever relative to saline infusions. Interestingly, inactivation of the medial PFC also significantly increased response latencies but only in the 25% and 12.5% probability blocks, where the relative long-term value of the Large/Risky option was comparable or less than that of the Small/Certain option (treatment × block interaction: $F(3,36) = 3.85, P < 0.05$, Dunnett’s, $P < 0.05$; Fig. 2A, middle panel). However, this effect was only apparent during free-choice trials, as analysis of the response latency data collected during forced-choice trials revealed no differences between treatment conditions ($F(1,12) = 1.89$, n.s.). There were no differences in the number of trial omissions or locomotor activity between saline and muscimol/baclofen treatments (all $F$s < 0.89, n.s.). Thus, under these conditions, inactivation of the medial PFC reduced risk discounting, leading to an apparent increase in risky choice.

**OFC**

A total of 16 rats were initially trained for this experiment. Five of these animals had placements that extended ventral to the OFC, and their data were excluded from the analyses. The remaining rats ($n = 11$) required an average of 28 days of training on the risk-discounting task prior to receiving counterbalanced infusions of saline or muscimol/baclofen into the OFC. Analysis of the choice data revealed no main effect of treatment ($F(1,10) = 0.38$, n.s.) or treatment × block interaction ($F(3,30) = 0.43$, n.s.; Fig. 2B, left panel). Although bilateral inactivation of the OFC had no effect on choice behavior, this manipulation did alter response latencies, as indicated by a significant treatment × block interaction ($F(3,30) = 4.26, P < 0.05$; Dunnett’s, $P < 0.05$; Fig. 2B, middle panel). Simple main effects analyses revealed that OFC inactivation did not affect response latencies during the 100% and 50% probability blocks, but significantly increased deliberation times in the latter 2 blocks, relative to saline infusions. As was observed from the medial PFC group, OFC inactivation did not affect response latencies during forced-choice trials ($F(1,10) = 3.48$, n.s.). There was also a slight decrease in locomotion following OFC inactivation ($1580 ± 229$) relative to saline treatment ($1712 ± 253$), but this difference failed to reach significance ($F(1,10) = 4.27, P = 0.07$). There was no effect of OFC inactivation on trial omissions ($F(1,10) = 1.79$, n.s.). Thus, inactivation of the OFC did not affect risky choice under conditions where rats were familiar with the relative risk/reward contingencies associated with different response options and changes in these contingencies that occurred over the course of a session.
Figure 2. Effects of inactivation of different PFC regions on risk discounting. The panels of each figure plots percentage choice of the Large/Risky lever (left) and response latencies (middle) as a function of the trial block (x-axis) following infusions of saline (white circles) or muscimol/baclofen (inactivation, black squares) into each of the 4 PFC subregions: (A) Medial PFC; (B) OFC; (C) anterior cingulate; and (D) insular cortex. Symbols represent mean ± standard error of the mean. Black stars denote a significant \( P < 0.05 \) main effect of treatment. White stars denote significant \( P < 0.05 \) differences between treatments during a specific block. Right panels are schematics of coronal sections of the rat brain showing the location of acceptable infusion placements through the rostral-caudal extent of each of the 4 PFC regions.
Anterior Cingulate

Thirteen rats were trained for this experiment. The data from 2 rats were excluded due to inaccurate placements and another rat died during surgery. The remaining 10 rats took an average of 33 days of training prior to receiving counterbalanced infusions of saline or muscimol/baclofen into the anterior cingulate. Inactivation of this region caused no discernable change in choice of the Large/Risky lever relative to saline treatment. This observation was confirmed by the lack of a significant main effect of treatment \((F(1,9) = 0.00, \text{n.s.})\) and treatment \(\times\) block interaction \((F(3,27) = 0.31, \text{n.s.; Fig. 2C, left panel})\). Likewise, response latencies during free-choice trials did not differ between treatment conditions (all \(F < 1.0, \text{n.s.}; Fig. 2C, middle panel\)). However, during forced-choice trials, rats displayed slightly longer response latencies following anterior cingulate inactivation \((1.3 \pm 0.1 \text{ s}), compared with saline infusions \((1.0 \pm 0.1 \text{ s}; F(1,9) = 11.26, P < 0.01)\). Locomotion and trial omissions were not altered significantly by anterior cingulate inactivations (all \(F < 1.0, \text{n.s.})\).

Insular Cortex

Thirteen rats were trained for this experiment, but data for 6 rats were excluded due to inaccurate placements. The remaining 7 rats took an average of 28 days of training on the risk-discounting task prior to surgery and receiving counterbalanced infusions of saline or muscimol/baclofen into the agranular insular cortex. Again, we observed no change in choice behavior following muscimol/baclofen infusions, as indicated by the lack of a significant main effect of treatment \((F(1,12) = 0.16, \text{n.s.})\), or treatment \(\times\) block interaction \((F(3,18) = 1.67, \text{n.s.; Fig. 2D, left panel})\). Insular inactivation did not significantly affect response latencies during either free-choice (Fig. 2D, middle panel) or forced-choice trials nor did it alter locomotion or trial omissions (all \(F < 2.51, \text{n.s.})\).

Medial PFC Inactivation (Ascending Probabilities)

Medial PFC inactivation increased selection of the Large/Risky lever when the probabilities of obtaining the larger reward decreased over the course of a risk discounting session. In a subsequent experiment, a separate group of 12 rats were trained for 25 days on a variant of this task, where the probability of obtaining the LR “increased” over the session, prior to receiving counterbalanced infusions of saline or muscimol/baclofen into the medial PFC. In contrast to the effects on choice behavior reported above, inactivation of the medial PFC induced the opposite effect on risk discounting under these conditions, with rats displaying a decreased preference for the Large/Risky lever over the 4 trial blocks. Analysis of these data revealed a significant main effect of treatment \((F(1,11) = 12.28, P < 0.05; \text{Fig. 3A})\). Rats chose the Large/Risky lever less often following medial PFC inactivations relative to saline infusions. There was no significant effect of inactivation on trial omissions or locomotion \((F < 2.5, \text{n.s.})\). However, there was a significant increase in average response latencies during free-choice trials across all the blocks after medial PFC inactivation \((F(1,11) = 8.82, P < 0.05; \text{Fig. 3B})\). Again, this effect was selective to trials where rats were required to choose between the 2 levers, as response latencies during forced-choice trials did not differ between treatments \((F(1,11) = 2.87, \text{n.s.})\).

Inspection of Figure 3A reveals that the decreased preference for the Large/Risky lever after inactivation of the medial PFC was apparent during the first trial block (12.5%) and persisted over the remainder of the session. However, the decreased choice of the Large/Risky lever during the first block was primarily attributable to 3 rats. We conducted a supplemental analysis on the data from the 9 remaining rats that displayed a comparable preference for the Large/Risky lever during the first trial block (i.e., matching for performance) after inactivation and saline treatments. In this instance, the analysis of these data again revealed a significant overall decrease in choice of the Large/Risky lever \((F(1,8) = 7.39, P < 0.05; \text{Fig. 3A, inset})\). Thus, in this subset of rats, even though medial PFC inactivation did not reduce preference for the Large/Risky lever during the first block, these animals were still slower to adjust their choice behavior as the probability of obtaining the larger reward increased over subsequent blocks. This suggests that the medial PFC may facilitate adjustments in preference

**Figure 3.** Effects of medial PFC inactivation on risk discounting with ascending probabilities. (**A**) Percentage of choice of the Large/Risky lever during free-choice trials following infusions of saline or muscimol/baclofen into the medial PFC for all 12 rats used in this experiment. Inactivation of the medial PFC decreased risky choice. Inset displays data from a subset of rats \((n = 9)\) that demonstrated comparable levels of choice of the Large/Risky lever after both saline and inactivation treatments during the initial, 12.5% probability block (i.e., matching for performance). (**B**) Response latencies displayed as a function of trial block. Black stars denote a significant \((P < 0.05)\) main effect of treatment. (**C**) Location of acceptable infusion placements for rats used in this experiment.
for the Large/Risky option in response to increases in the probability of obtaining the larger reward.

Experiment 2: Effects of Medial PFC Inactivation on Performance of a Within-Session Reversal

Inactivation of the medial PFC (but not other frontal lobe regions) induced differential effects on risk discounting depending on the manner in which the probabilities of obtaining the larger reward changed over a session. When the odds of the Large/Risky reward were initially 100% and then decreased, medial PFC inactivation increased risky choice, whereas when the probabilities were initially low and subsequently increased, similar inactivations reduced preference for the Large/Risky lever. Both variants of this task require a shift in the direction of responding, whereby rats choose the Large/Risky lever less or more often as the probabilities decrease or increase over the session, respectively. Thus, one potential interpretation of the effects of medial PFC inactivation on risk discounting may be that these manipulations impaired behavioral flexibility, such that rats were perseverating on the lever that they preferred during the first block (Large/Risky or Small/Certain). Notably, similar inactivations of the medial PFC do not impair performance of standard or probabilistic reversal tasks, although they do impair shifting between discrimination strategies (Ragozzino et al. 1999; Block et al. 2007; Ragozzino 2007; Floresco, Block, and Tse 2008). Nevertheless, we conducted a subsequent experiment to determine whether alterations in risk-based decision making induced by medial PFC inactivations were due to perturbations in response flexibility. Rats were trained on a modified within-session reversal task that was similar to the risk-discounting procedure in a number of respects.

Materials and Methods

Within-Session Reversal Task

Rats underwent initial lever-pressing training in a manner identical to that described in Experiment 1. They then received daily training sessions consisting of 56 trials, separated into 2 blocks of 28 trials. The 2 blocks were each comprised of 8 forced-choice trials where only one lever was presented (4 trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever. This was followed by 20 free-choice trials, where both levers were presented (i.e., 40 free-choice trials in total, as in the risk-discounting task). Each 38-min session began in darkness with the LR lever on the vast majority of free-choice trials, which continued to deliver 1 pellet. This pattern of choice was not altered by medial PFC inactivation. Analysis of the choice data revealed a significant main effect of block ($F(1,6) = 103.16, P < 0.001$) but no significant main effect of treatment ($F(1,6) = 0.84, n.s.$) or treatment x block interaction ($F(1,6) = 2.75, n.s.$; Fig. 4A). Interestingly, in this experiment, there were no effects of medial PFC inactivations on response latencies ($F(1,6) = 0.01, n.s.$). Likewise, locomotion and trial omissions did not differ between treatment conditions (all $F$s < 0.9, n.s.). The location of acceptable medial PFC infusion placements in this experiment is displayed in Figure 4B. Thus, medial PFC inactivation did not impair the ability to perform a within-session reversal in response to changes in reinforcement contingencies. This suggests that alterations in risk discounting induced by medial PFC inactivation cannot be easily attributed to a general impairment in response flexibility.

Experiment 3: Effects of Inactivation of the Medial PFC on Risk Discounting with Fixed Probabilities

Another potential explanation for the alterations in risk discounting observed in Experiment 1 may be that medial PFC inactivation disrupted monitoring of “changes” in the probability of obtaining the larger reward that occurred within a session. Alternatively, this manipulation may have induced a more fundamental disruption in calculating the relative value of the Large/Risky option within each trial block. To assess this latter hypothesis, a separate group of rats were trained on a simplified version of the task, in which the probability of obtaining the larger reward remained constant throughout a session. Initially, the probability was fixed at 40%, making the relative long-term value of the Large/Risky option (4 pellets @ 40%) higher than the Small/Certain option (1 pellet @ 100%). Rats were then retrained and tested under conditions where the probability of obtaining 4 pellets was set at 10%. In this instance, selection of the Small/Certain option would yield a greater amount of reward in the long term.
Eight rats underwent initial lever-pressing training in a manner identical to that described in Experiment 1. They were then trained on the modified risk discounting procedure, consisting of 40 trials, broken down into 20 forced-choice, followed by 20 free-choice trials. Each session took 26 min to complete. All other aspects of the task were identical to the risk-discounting task used in Experiment 1. On each trial, selection of the Large/Risky lever delivered 4 pellets with a 40% probability, whereas pressing the Small/Certain lever delivered 1 pellet with 100% probability. The 40% probability was chosen to maximize the possibility of detecting either increases or decreases in the preference for the Large/Risky lever, given our observation in Experiment 1 that rats tend to select the Large/Risky lever on ~90% of trials when the probability of obtaining 4 pellets was higher (i.e., 50%; e.g., see Fig. 2A). Rats were trained 6–7 days a week until, as a group, they chose the Large/Risky lever on at least 60% of successful trials and demonstrated stable performance for 3 consecutive days. They were then subjected to surgery, retraining, and their first sequence of intracranial microinfusions.

Following the first set of microinfusion test days, rats were retrained on the same task for another 11 days but with the probability of obtaining the larger reward now set to 10%. This probability was chosen because it biases rats to use a risk-averse strategy but was large enough to ensure that, over 20 forced-choice trials, rats will experience at least some reward so that the probability would not be inferred to be 0%. By the end of this training period, rats as a group chose the Large/Risky lever on less than 40% of the free-choice trials and demonstrated stable performance for 3 consecutive days. They then received a second series of counterbalanced infusions into the medial PFC.

**Materials and Methods**

**Risk Discounting with Fixed Probabilities**

Eight rats underwent initial lever-pressing training in a manner identical to that described in Experiment 1. They were then trained on the modified risk discounting procedure, consisting of 40 trials, broken down into 20 forced-choice, followed by 20 free-choice trials. Each session took 26 min to complete. All other aspects of the task were identical to the risk-discounting task used in Experiment 1. On each trial, selection of the Large/Risky lever delivered 4 pellets with a 40% probability, whereas pressing the Small/Certain lever delivered 1 pellet with 100% probability. The 40% probability was chosen to maximize the possibility of detecting either increases or decreases in the preference for the Large/Risky lever, given our observation in Experiment 1 that rats tend to select the Large/Risky lever on ~90% of trials when the probability of obtaining 4 pellets was higher (i.e., 50%; e.g., see Fig. 2A). Rats were trained 6–7 days a week until, as a group, they chose the Large/Risky lever on at least 60% of successful trials and demonstrated stable performance for 3 consecutive days. They were then subjected to surgery, retraining, and their first sequence of intracranial microinfusions.

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**Surgery, Microinfusions, and Histology**

Rats were implanted with bilateral guide cannulae into the medial PFC as described in Experiment 1. All other procedures were identical to those described in Experiment 1.

**Results**

Rats were trained for 24 days prior to receiving the first sequence of counterbalanced infusions of muscimol/baclofen or saline into the medial PFC. Of the initial 8 rats, one died after surgery, and the infusion placement for another was outside the boundary of the prelimbic cortex. Its data were excluded from the analyses. Following saline infusions, the remaining 6 rats displayed a slight preference for the Large/Risky option when the probability of obtaining 4 pellets was 40%, selecting this lever on ~60% of free-choice trials (Fig. 5A, left panel). Importantly, inactivation of the medial PFC did not alter this preference ($F(1,5) = 0.40$, n.s.; Fig. 5A left panel). There were also no differences between treatment conditions in terms of locomotion, omissions, or response latencies (all $F$'s < 2.0, n.s.).

Rats were subsequently retrained for another 11 days with the probability of obtaining the Large/Risky reward set at 10%. By the end of this retraining period, rats were selecting the Large/Risky lever less often, compared with their performance when the probability was set at 40% (Fig. 5, inset). Analysis of the choice data obtained from the last 3 baseline days prior to the first (40% chance of the Large/Risky reward) and second (10% chance) infusion tests days confirmed that rats significantly discounted the Large/Risky lever as the probability of reward was reduced ($F(1,5) = 7.82$, $P < 0.05$). Again, inactivation of the medial PFC failed to alter choice behavior ($F(1,5) = 3.91$, n.s.; Fig. 5A right panel), locomotion, omissions, or response latencies relative to saline infusions (all $F$'s <1.9, n.s.). The location of acceptable medial PFC infusion placements in this experiment is displayed in Figure 5B. Thus, inactivation of the medial PFC does not alter choice between small/certain and larger/uncertain rewards when the relative value of larger, probabilistic rewards remains constant during a session.

**Discussion**

The major finding of the present study is that inactivation of the prelimbic region of the medial PFC induces dramatic effects on risky choice assessed with a probabilistic discounting task. However, the specific effect of medial PFC inactivation was dependent on the manner in which the reward probabilities changed over a session. When the probabilities associated with the Large/Risky option were initially high (100%) and subsequently decreased, medial PFC inactivations increased risky choice. Yet, when the 4-pellet option was initially disadvantageous (12.5%) and then increased in value, similar
inactivations had the opposite effect. Subsequent experiments indicated that these effects were not easily attributable to general disruptions in response flexibility or to evaluating the relative value of larger/uncertain versus smaller/certain rewards. In contrast, inactivation of the OFC did not affect risk discounting but did increase response latencies during the latter portion of the session. Similar inactivations of the anterior cingulate or insular cortex did not reliably alter choice behavior. Collectively, these findings indicate that the medial prelimbic PFC plays a critical role in guiding choice between certain and uncertain rewards of different magnitudes in response to changes in reward probability.

Involvement of the Rat Medial PFC in Risk Discounting

At first glance, the increase in risky choice induced by medial PFC inactivation in Experiment 1 may have indicated that this region normally biases choice toward small, certain rewards. However, similar inactivations had the opposite effect when the probabilities of obtaining the Large/Risky reward were initially low and then increased, suggesting that this relatively simple explanation is insufficient to account for our findings. Alternatively, it is possible that these treatments may have induced a general impairment in response flexibility, given that in both experiments, rats persisted in selecting the lever they displayed a bias for during the first probability block. It is notable that following medial PFC inactivations, rats were able to adjust choice of the Large/Risky lever in response to changes in reward probability, albeit at a slower rate than that displayed after saline treatments. Nevertheless, we conducted a subsequent experiment where rats were required to perform a within-session reversal, patterned after the risk-discounting task. Responding on 1 of 2 levers initially delivered a large 4-pellet (LR) or smaller 1-pellet (SR) reward. In the latter part of the session, the LR lever no longer delivered food, but the SR lever continued to deliver 1 pellet. If medial PFC inactivations induced a general tendency to perseverate toward the lever they initially displayed a bias for at the beginning of a session, we would have expected to observe an impaired ability to shift choice between levers after the reversal. However, this effect was not observed, arguing against the notion that the results of Experiment 1 were attributable to impairments in response flexibility. These results are in keeping with numerous other studies showing that inactivation of the prelimbic region of the medial PFC does not affect reversal learning (Ragazzino et al. 1999; Birrell and Brown 2000; Floresco, Block, and Tse 2008).

The preliminary PFC has been implicated in guiding goal-directed behavior in response to changes in the value of rewards linked to particular actions (Balleine and Dickinson 1998; Killcross and Coutureau 2003). Experiment 3 examined whether medial PFC inactivations interfered with choice behavior when the relative long-term value of larger, probabilistic rewards remained constant throughout a session. Here, the probability of obtaining 4 pellets was fixed so that over 20 free-choice trials, this option either had a greater (40% = ~32 pellets) or lesser (10% = ~8 pellets) long-term value than the certain, 1 pellet option (20 pellets). Following saline infusions, rats displayed an appropriate bias toward the Large/Risky or Small/Certain lever when the odds of obtaining the larger reward were 40% or 10%, respectively. Importantly, inactivation of medial PFC did not alter choice behavior under either condition. This suggests that the medial PFC is not critical for basic estimations of reward probabilities when animals must evaluate the relative long-term value associated with smaller, certain versus larger, uncertain rewards. Moreover, this lack of effect on choice indicates that the decreased choice of the Large/Risky option following medial PFC inactivations observed in Experiment 1 (i.e., risk discounting with ascending probabilities) cannot be attributed to a general reduction in preference for larger, probabilistic rewards. Rather, it appears that this region plays a more specialized role in biasing choice in response to changes in the probabilities of obtaining larger, uncertain rewards.

Further insight into the contribution of the medial PFC to risk-based decision making comes from a discussion of how rats may identify changes in reward probabilities to facilitate risk discounting. Over repeated training, animals learn that changes in the probabilities associated with the Large/Risky reward are signaled by intermittent blocks of forced-choice trials that precede each set of 10 free-choice trials. Thus, rats must remember the outcomes of previous trials and use this information to update their representation of the relative value associated with the Large/Risky lever as a session proceeds.
Rats may also use internal temporal cues to estimate the relative value of the Large/Risky option, as they are trained that the likelihood of obtaining 4 pellets early in a session is substantially different from that later in a session (Catania 1970). There is some suggestion that damage to the medial PFC impairs aspects of time perception (Dietrich and Allen 1998; Thorpe et al. 2002) and induces insensitivity to within-session shifts in delays in a delay-discounting task (Cardinal et al. 2001). Thus, in this context, the medial PFC may subserve an “updating function,” whereby mnemonic and temporal information used to identify changes in reward probabilities is integrated to adjust the direction of behavior to maximize reward. Following inactivation of the medial PFC, rats were impaired at using within-session cues to update their choice according to the reward contingencies of the current trial block. Therefore, dysfunction in this region may limit the ability to use internally generated information to update representations of expected reward probabilities based on recently experienced events.

The rat medial PFC displays anatomical connectivity homologous to the ventral portion of the anterior cingulate (Area 32) in primates (Uylings and van Eden 1990) and recent studies suggest that this region plays an important role in mediating risk-based decisions in humans. General increases in activity in this region are observed when healthy subjects perform common cost–benefit decision-making tasks (Ernst et al. 2002; Labudda et al. 2008; Lawrence et al. 2009), particularly when they make risky relative to safe choices on the Iowa gambling task (Lawrence et al. 2009). Similarly, using a task where the risk associated with the different choices was “not winning” a given reward (as in the task used in the present study), Smith et al. (2009) found greater activation in the ventral anterior cingulate (Area 32) during risky versus safe choices, as well as during low-probability versus high-probability choices. Moreover, patients with ventromedial PFC lesions that include damage to Area 32 show impaired decision making on the Cambridge Gamble Task (Clark et al. 2008). Yet, the rat medial PFC has also been proposed to share “functional” homology to the dorsolateral PFC of primates (Brown and Bowman 2002; Uylings et al. 2003). For example, the medial and lateral PFCs have been implicated in working memory in rats (Seamans et al. 1995; Floresco et al. 1999), and humans (Owen et al. 1990; Stuss and Alexander 2000), respectively. In humans, dorsolateral PFC activity has been linked to changes in contexts associated with different gains and losses of reward, particularly when outcomes are the opposite of expectations (Akitsuki et al. 2003). Activity in this region is also increased during performance of the Iowa gambling task (Ernst et al. 2002), particularly in the decision phase (Labudda et al. 2008). Likewise, damage to the dorsolateral PFC has been associated with impairments in different forms of risk-based decision making (Manes et al. 2002; Brand et al. 2004; Fellows and Farah 2005). These findings, viewed in light of the present data, suggest that with respect to risk-based decision making, the medial PFC of the rat may share functions that are similar to those mediated by both the ventral anterior cingulate cortex and dorsolateral PFC in humans.

**The Role of Other PFC Regions in Cost-Benefit Decision Making**

Inactivation of the OFC did not affect risk discounting, although these manipulations dramatically increased response latencies in a manner similar to that induced by medial PFC inactivation, whereby deliberation times were increased only in the last 2 trial blocks. This effect on response latencies was only apparent during free-choice trials when rats had to choose 1 of the 2 response options. Notably, it is during these blocks that the relative long-term value of the Large/Risky option switched from having a greater value (100% and 50%) to roughly equal (25%) or lesser (12.5%) value than the Small/Certain option. This suggests that although the OFC may not be necessary for making advantageous choices involving risks and rewards under these conditions, neural activity in this region may aid speed of processing about the cost–benefit contingencies associated with each decision following shifts in the relative long-term values of probabilistic rewards. Consistent with these findings, patients with OFC damage also display increased deliberation times when performing certain risk-based decision making tasks (Rogers, Everitt, et al. 1999; Manes et al. 2002; Clark et al. 2008).

Our finding that inactivation of the OFC did not alter risk discounting was somewhat surprising, considering previous studies with both rodents and humans that have implicated this region in cost–benefit decision making tasks about risks and rewards (Rogers, Everitt, et al. 1999; Rogers, Owen, et al. 1999; Manes et al. 2002; Clark et al. 2003, 2008; Ernst et al. 2004; Fukui et al. 2005). Lesions of the rat OFC induced prior to training led to a reduced preference for larger probabilistic rewards (2 pellets) relative to a smaller certain reward (1 pellet; Mobini et al. 2002). In that study, the larger reward probability remained constant over a daily session and was decreased systematically every 20–25 days. The “risk-averse” tendencies displayed by OFC lesioned rats were most prominent when the relative long-term value of the larger, probabilistic option (32% or 20%) was less than that of the small certain option. This suggests that OFC lesions may impair learning about the relative value of larger, probabilistic rewards. This notion is supported by findings from human neuroimaging studies, where lateral OFC activity is associated with learning risk/reward contingencies of the Iowa Gambling task over a session (Lawrence et al. 2009). In contrast, rats in the present study were trained for 3–4 weeks until they demonstrated stable patterns of risk discounting, implying that they had learned to adjust their choice behavior in response to within-session changes in reward probabilities. Thus, the lateral aspects of the OFC may facilitate the initial learning of risk/reward contingencies, but neural activity in this region may not be required to guide decision making once these contingencies have been acquired.

It is notable that patients with OFC damage also display impaired decision making on tasks where subjects are explicitly informed of reward probabilities prior to making a choice (Clark et al. 2008), similar to the task used in the present study, where rats were familiarized with changes in reward probability over many training days. However, in that study, the patient group that showed impairments included those with damage to the medial portions of the OFC. In fact, a lesion control group that included individuals with lateral OFC damage performed similar to healthy controls. Thus, it may be that the medial, rather than the lateral OFC, plays a more prominent role in facilitating risk-based decisions in situations where subjects have prior knowledge about reward probabilities.

Damage to the insular cortex in humans has been associated with alterations in risk-related judgments (Bar-On et al. 2003;
Clark et al. 2008). These patients are able to make advantageous decisions (i.e., they correctly choose options yielding the most reward), but do not adjust their betting according to gain-loss probability, suggesting that they are less "risk sensitive" than healthy controls. In a similar vein, imaging studies in healthy controls suggest that the insular cortex may have a specific role in using negative outcomes (i.e., punishment) to bias choice behavior to maximize potential reward (O’Doherty et al. 2003; Cohen et al. 2008; Preuschoff et al. 2008). In contrast, we did not observe significant alterations in risk discounting following insular cortex inactivation. Note that the task used in the present study measured whether rats were able to choose the most advantageous option based on changing reward probabilities. However, our procedures did not employ any explicit punishments per se; the risk was a lost opportunity to obtain a reward, which may explain the lack of effect on risk discounting following inactivation of this region. Thus, it would be of particular interest to investigate the role of the rat insular cortex in guiding decision making when animals evaluate potential aversive consequences associated with different options.

Inactivation of the dorsal anterior cingulate cortex also did not affect risk discounting, even though infusions of GABA agonists into the adjacent prelimbic cortex did affect choice and response latencies. These 2 regions of the medial PFC receive dissociable patterns of innervation from the mid-dorsal thalamus (Conde et al. 1990) and also exhibit different afferent and efferent connectivity with other cortical and subcortical structures (Sesack et al. 1989; McDonald 1991; Heidbreder and Groenewegen 2003). The present findings suggest that despite their close proximity, these 2 cortical regions have dissociable functions. This notion is in keeping with numerous studies demonstrating that lesions or inactivation of the prelimbic versus anterior cingulate cortex induce differential effects on cognitive, executive, and decision-making functions (Seamans et al. 1995; Bussey et al. 1997; Walton et al. 2003).

It is interesting to compare the present findings with previous studies on the dissociable contribution of rat PFC subregions to other forms of cost-benefit decision making, such as delay or effort discounting. The OFC appears to play a role in delay discounting, guiding choice between larger, delayed versus smaller, immediate rewards, whereas lesions of the anterior cingulate do not interfere with this form of decision making (Cardinal et al. 2001; Mobini et al. 2002; Winstanley et al. 2004; Rudebeck et al. 2006). Conversely, the anterior cingulate, but not the OFC, is a component of the circuitry underlying effort-related decisions, but not delay discounting (Walton et al. 2003; Rudebeck et al. 2006; Floresco and Ghods-Sharifi 2007; but see Schweimer and Hauber 2005). Notably, medial PFC lesions do not significantly alter cost-benefit judgments involving either delay- or effort-related costs (Cardinal et al. 2001; Walton et al. 2003). Our findings that the prelimbic PFC (but not the OFC or anterior cingulate) contributes to guiding choice between certain and probabilistic rewards further supports the notion that different response costs (e.g., delays, effort, and uncertainty) are processed by separate frontal lobe regions (Rudebeck et al. 2006; Floresco, St Onge, et al. 2008). It is important to highlight that with delay or effort discounting procedures, animals typically obtain "some" reward after each choice, receiving immediate feedback about the costs associated with larger rewards. Imposition of these costs may reduce the perceived value of larger rewards, biasing choice toward smaller but more easily obtainable rewards. On the other hand, risk discounting requires monitoring of rewarded and nonrewarded outcomes, as well as integration of this information over many trials to estimate the long-term value of small/certain versus large/uncertain rewards. In turn, this information may be incorporated in computations about the probability of obtaining the larger reward under conditions where reward probabilities change. Thus, the seemingly selective involvement of the medial PFC in this form of discounting may be linked to its role in the temporal organization of behavior (Fuster 2000), whereby internally generated information is used to keep track of changes in reward probabilities and update value representations that, in turn, may facilitate efficient decision making.

**Funding**

Canadian Institutes of Health Research (MOP-89861 to S.B.F., a Michael Smith Foundation for Health Research Senior Scholar); Natural Sciences and Engineering Research Council of Canada and the Michael Smith Foundation for Health Research (to J.R.S.O.).

**Notes**

We are grateful to Ying Zhang for her assistance with behavioral testing and surgical procedures and Colin Stopper for his helpful comments on the manuscript. *Conflict of Interest.* None declared.

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