

Contributions of the orbitofrontal cortex to impulsive choice: interactions with basal levels of impulsivity, dopamine signalling, and reward-related cues

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Abstract

Rationale Individual differences in impulsive decision-making may be critical determinants of vulnerability to impulse control disorders and substance abuse, yet little is known of their biological or behavioural basis. The orbitofrontal cortex (OFC) has been heavily implicated in the regulation of impulsive decision-making. However, lesions of the OFC in rats have both increased and decreased impulsivity in delay-discounting paradigms, where impulsive choice is defined as the selection of small immediate over larger delayed rewards.

Objectives Reviewing the different methods used, we hypothesized that the effects of OFC inactivation on delay discounting may be critically affected by both subjects' baseline level of impulsive choice and the presence or absence of a cue to bridge the delay between selection and delivery of the large reward.

Results Here, we show that OFC inactivation increased impulsive choice in less impulsive rats when the delay was cued, but decreased impulsive choice in highly impulsive rats in an uncued condition.

Conclusions Providing explicit environmental cues to signal the delay-to-reinforcement appears to change the way in which the OFC is recruited in the decision-making process in a baseline-dependent fashion. This change may reflect activation of the dopamine system, as intra-OFC

infusions of dopamine receptor antagonists increased impulsive choice but only when the delay was cued.

Keywords Delay discounting · Dopamine · Eticlopride · Impulsivity · Incentive salience · SCH 23390 · Antagonist · Baclofen · Muscimol · Prefrontal cortex · Behaviour · Rat

Introduction

Abnormal levels of impulsivity are associated with a wide range of psychiatric disorders including attention deficit hyperactivity disorder (ADHD), addiction, and pathological gambling. The orbitofrontal cortex (OFC) has been implicated in these disorders as well as in the performance of laboratory tests of impulsive decision-making and gambling (Bechara et al. 1999, 2000; Bolla et al. 2003; Coffey et al. 2003; Damasio 1994; Rogers et al. 1999; Scheres et al. 2008). A widely used model of impulsive decision-making in both humans and laboratory animals is the delay-discounting task (Ainslie 1975; Evenden and Ryan 1996). Here, impulsive choice is defined as a preference for smaller immediate over larger delayed rewards and is thought to reflect intolerance to delay-of-gratification. In rodents, bilateral OFC lesions have been reported to both increase (Mobini et al. 2002; Rudebeck et al. 2006) and decrease (Winstanley et al. 2004) impulsive choice. Understanding the neurobiological basis for such discrepancies may illuminate our understanding of how delay discounting engages the OFC.

One of the key variables within delay-discounting tasks is the signalling of the delay. Increasing the delay between response and reinforcement decreases the strength of the resulting response-reward association. Signalling the duration of the delay with a cue can facilitate learning and

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increase the effective value of the delayed reward, as the cue acquires some of the affective properties of the reward and may act as a conditioned reinforcer (Mazur 1997; Williams and Dunn 1991). In both studies in which OFC lesions increased impulsive choice, it could be argued that cues bridged the delay between response and reinforcement: in a two-lever choice paradigm, a cue light was illuminated for the duration of the delay (Mobini et al. 2002), whereas when a T-maze apparatus was used, gates were lowered in front of and behind the subject, thus confining the subject for the duration of the delay (Rudebeck et al. 2006). Inadvertently, the signals associated with this confinement (e.g. raising and lowering of gates, restricting exploration to one part of the maze), although less discrete than a cue light, may have likewise acted to cue the delay. In contrast, OFC lesions enhanced choice of the larger delayed reward when no such cues were present (Winstanley et al. 2004). Hence, the presence of cues that signal the delay could alter the means in which the OFC is recruited during delay discounting (Floresco et al. 2008a).

Presentation of conditioned cues increases the release of dopamine (DA) (Phillips et al. 2003; Schultz et al. 1997), and recent evidence suggests that dopaminergic innervation of the OFC plays an important role in mediating delay-discounting judgements. The OFC receives dopaminergic input from its direct connections with the ventral tegmental area (Dunnett and Robbins 1992; Oades and Halliday 1987). In vivo microdialysis data indicate that DA turnover increases within the OFC when animals are performing delay-discounting judgements (Winstanley et al. 2006), and depleting DA within the OFC affects the rate of delay discounting observed (Kheramin et al. 2004). DA is heavily implicated in impulse control disorders, and the therapeutic effects of amphetamine in ADHD have been largely attributed to its ability to potentiate dopaminergic signalling (Bradley 1937; Cormier 2008; Feldman et al. 1997; Fleckenstein et al. 2007). Amphetamine has previously been shown to decrease impulsive decision-making on delay-discounting tasks (Barbelivien et al. 2008; de Wit et al. 2002; Floresco et al. 2008b; Monterosso et al. 2007; van Gaalen et al. 2006; Wade et al. 2000; Winstanley et al. 2003b, 2005) and potentiate responding for conditioned reinforcers (Hill 1970; Robbins 1976). In contrast, systemic administration of DA antagonists increases impulsive choice, although the relative roles of the D₂-like vs. D₁-like receptors are still unclear (Floresco et al. 2008b; van Gaalen et al. 2006; Wade et al. 2000). However, recent evidence indicates that decreasing dopaminergic activity at D₁ receptors within the medial prefrontal cortex increases impulsive decision-making (Loos et al. 2010). Hence, DA release may be increased during the delay-to-reward period, particularly when a conditioned cue is present, and this may promote choice of the larger delayed rewards through its effects in the OFC.

The current experiments aimed to explore the nature of these relationships by investigating whether signalling the delay affected the contribution of the OFC to delay discounting. Furthermore, the involvement of dopaminergic signalling was ascertained through the local infusion of D₁ and D₂ receptor antagonists. We hypothesized that animals tested in the presence of a cue would be less impulsive and that inactivation of the OFC as well as regional infusion of dopamine antagonists would increase impulsive choice. In contrast, we predicted that inactivating the OFC of animals trained without a cue would decrease impulsive choice in parallel to previously published data and that dopaminergic agents would have less effect.

Methods and materials

Subjects

Subjects were 32 male Long-Evans rats (Charles River Laboratories, St. Constant, Quebec, Canada) weighing 275–300 g at the start of the experiment and maintained on 14 g rat chow per day. Water was available ad libitum. All animals were pair-housed in a colony room under a reverse 12-h light–dark cycle (lights off at 8:30 am) maintained at a temperature of 21°C. Testing and housing was in accordance with the 1996 edition of the “Guide for the Care and Use of Laboratory Animals” (NIH) and approved by the Canadian Council of Animal Care and the Animal Care Committee of the University of British Columbia.

Behavioural testing

Apparatus Testing took place in standard operant chambers (30.5×24×21 cm; Med-Associates, St. Albans, VT, USA). Each chamber was enclosed in a sound-attenuating box and equipped with a fan to provide ventilation and mask any extraneous noise. Operant chambers also contained two retractable levers, one located on each side of a central food magazine with a round 2.8-W stimulus light located 1 cm above each lever. Food reinforcement (sucrose pellets, 45 mg; Bioserv, Frenchtown, NJ, USA) was delivered by a pellet dispenser into a food cup. Chambers could be illuminated with a single 100-mA houselight located in the top centre of the wall opposite the levers. A photobeam was located across the mouth of the food magazine to enable detection of nosepoke responses. All experimental data were recorded by an IBM personal computer connected to the chambers via an interface using MedPC-IV software (Med-Associates, St. Albans, VT, USA).

Habituation and lever training Training methods are adapted from Cardinal et al. (2000) and have been

previously described elsewhere (Floresco et al. 2008b). Animals received sucrose pellets in their home cage 1 day prior to their first day of training. Before placing the animals into the operant chamber on the first day of training, two to three pellets were placed in the food cup and on the active lever. In the first stage of training, rats were trained to respond on the levers for sucrose pellets under a fixed-ratio 1 schedule to a criterion of 50 lever presses in 30 min. Once this criterion was met for a single lever, animals were trained on the opposite lever to the same criterion (counterbalanced left/right between subjects). Following successful completion of this training stage, animals were trained to respond on each lever within 10 s of the lever being extended. These training sessions consisted of 90 trials and began with both levers retracted and the chamber in darkness. A trial began with illumination of the houselight, then extension of one lever 3 s later. If the rat pressed the lever within 10 s, the lever retracted and one sucrose pellet was delivered into the food magazine. The houselight then remained on for 4 s, after which the chamber entered an inter-trial interval (ITI) state with the houselight off for the remainder of the trial. An omission was scored if the animal failed to respond in 10 s, at which point the lever retracted and the chamber entered the ITI state. Each trial lasted for 40 s, with no more than two consecutive presentations of the same lever. Animals were trained to a criterion of 80 or more successful trials

per session, which was achieved within six to seven sessions.

Delay discounting An outline of the delay-discounting task outline is provided in Fig. 1. Each session lasted 56 min and consisted of 4 blocks of 12 trials. Each trial lasted 70 s regardless of lever choice, and each block began with two forced choice trials where only one of the two levers was extended (one trial for each lever, presented randomly), followed by ten free choice trials where both levers were extended. A trial began with the illumination of the houselight and extension of the lever(s) 2 s later. As in lever training, if the rat failed to respond within 10 s, the trial was scored as an omission, the lever(s) retracted, and the chamber entered the ITI state with the houselight off until the next trial was scheduled to begin. Responding on one lever (lever A) always provided a small immediate reward of one pellet, the other (lever B) a large reward of four pellets. The location of levers A and B were counterbalanced between subjects. Pellets were delivered 0.5 s apart. After reward delivery, the houselight remained on for another 4 s, after which the chamber entered the ITI state for the duration of the trial.

In the No Cue group, both levers resulted in immediate rewards for all trials in the first three sessions. Following this training animals were tested on the delay-discounting program, where a response on either lever resulted in an immediate reward for the first block of trials. In the

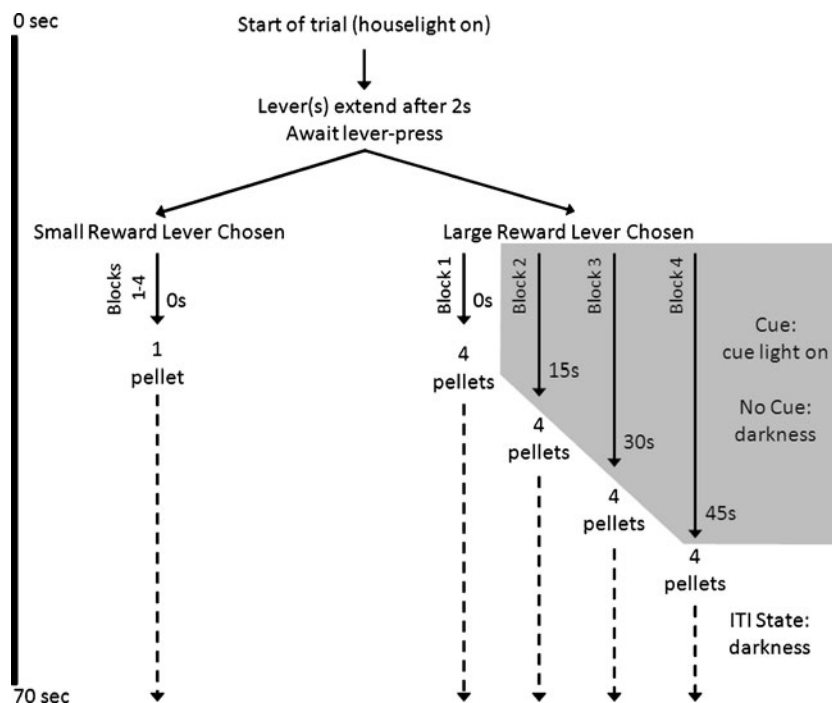


Fig. 1 The delay-discounting task. In the cue version of the task, the cue light is illuminated during the delay to the large reward when the large reward lever is chosen during blocks 2, 3, or 4, then immediately

turned off upon reward delivery. When no cue is present, the operant chamber remains in darkness during this delay

following blocks, the delay to the large reward increased in 15 s intervals, such that in the second block, a response on lever B resulted in a reward of four pellets after a 15 s delay. The delay in the third block was 30 s, then 45 s in the fourth block. Throughout the duration of the delay, the chamber remained in darkness as in the ITI state. Animals in the Cue group were trained on the same delay-discounting program as in the No Cue group; however, the cue light located above lever B was illuminated immediately after a response on lever B was made and remained on until reward delivery, signalling the duration of the delay. Daily training sessions continued 5 days per week until stable baseline behaviour was achieved, as indicated by non-significant effects of session and session \times delay when choice of the large delayed reward was analysed across five sessions by ANOVA (see 'Data analysis' section for further details of ANOVA structure; No Cue group: 35 sessions, Cue group: 22 sessions).

Surgery

Rats were anesthetized with ketamine (Ketaset, 100 mg/kg i.m.; Vetoquinol, Lavaltrie, Quebec, Canada) and xylazine (Rompun, 10 mg/kg i.m.; UBC Animal Care Centre, Vancouver, British Columbia, Canada) and secured in a stereotaxic frame with the incisor bar set at -3.3 for a flat skull position. Bilateral 22-gauge, stainless steel cannulae (Plastics One, Roanoke, VA, USA) were implanted into the OFC and secured to the skull using three bone screws and dental cement. Stereotaxic coordinates used were: anteroposterior (AP) $+3.8$ (from bregma), medial (M) ± 2.6 , and dorsoventral (DV) -2.9 from dura (Paxinos and Watson 1998). Twenty-nine gauge obdurators, flush with the end of the guide cannulae, joined to plastic dust caps (Plastics One, Roanoke, VA, USA) were then inserted to protect the head assembly. Animals were allowed to recover for 1 week before behavioural testing resumed.

Microinfusion procedure

Infusion methods were adapted from a previously published report (Winstanley et al. 2003a). Once a stable post-operative baseline was established (five to seven sessions), rats were habituated to the infusion procedure with two mock infusions. Infusions were given in a 3-day cycle, starting initially with a baseline session. The following day, rats received a drug or saline infusion prior to testing. On the third day, animals were not tested and remained in their home cages. The minimum interval between infusions was therefore 3 days.

During infusions, rats were gently restrained whilst obdurators were removed and a 29-gauge injector extending 1 mm beyond the length of the guide cannulae was inserted into each guide. A volume of 0.5 μ l of solution was

infused using a dual channel infusion pump (Harvard Apparatus, Holliston, MA, USA) at a rate of 0.25 μ l/min, after which the injector was left in place for 1 min to allow for the drug to diffuse in the local vicinity of the injector tip. The injectors were then removed and obdurators were replaced. Rats were then placed in cages similar to their home cages in a quiet holding area for 10 min before being placed into the operant chambers and the delay-discounting task started. All infusions were administered in a behavioural testing room separate from the operant testing room.

For all animals, the first two bilateral infusions received were either saline or a cocktail of the GABA_A receptor agonist muscimol and the GABA_B receptor agonist baclofen (0.125 μ g of each compound in 0.5 μ l) according to a counterbalanced design. After these two microinfusion sessions, the Cue and No Cue groups were split in half. One group of 16 rats (8 Cue and 8 No Cue animals) received microinfusions of the D₂ receptor antagonist eticlopride (0.1, 0.3, and 1.0 μ g/side). The other 16 animals received microinfusions of the D₁ receptor antagonist SCH 23390 (0.1, 0.3, and 1.0 μ g/side). The order in which doses of both antagonists were administered was counterbalanced according to a Latin square design. At least 1 week elapsed between infusions of the GABA agonist cocktail and infusions of the DA receptor antagonists. Individuals' performance of the task during this time did not differ from their post-operative baseline, suggesting that infusion of the GABA agonists had not caused long-term changes in OFC function.

Drugs

All drugs were purchased from Sigma-Aldrich (Oakville, ON, Canada) and prepared fresh on each microinfusion day. Baclofen hydrochloride and muscimol hydrobromide were each dissolved separately in saline at a concentration of 0.5 mg/ml each, then mixed together in equal amounts for a final concentration of 0.25 mg/ml of each compound. Eticlopride hydrochloride and SCH 23390 hydrochloride were dissolved in saline to 2.0 mg/ml, then diluted with saline to their final concentrations.

Data analysis

Statistical analysis was conducted using SYSTAT for Windows (version number 12.00.08; SSI, Chicago, IL, USA). The primary variable analysed was the number of large reward (lever B) choices, excluding forced choice trials. The number of omissions was analysed as a separate variable. An arcsine transformation was performed for these data prior to statistical analysis in order to limit the effect of an artificially imposed ceiling (i.e. ten choices per block). The latency to respond on the levers (free choice trials only) was also analysed. Data were subjected to a two-way,

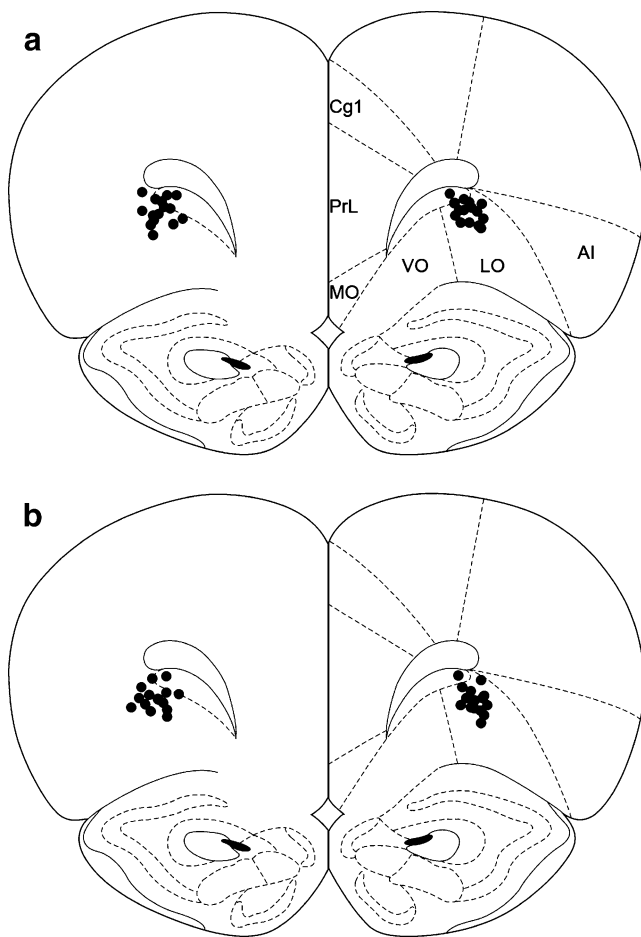


Fig. 2 Location of injector tips within the OFC in the **a** No Cue and **b** Cue groups

repeated-measures analysis of variance (ANOVA) with session, or drug dose, and delay as the within-subjects factors. If analyses produced significant effects of drug dose ($p < 0.05$), values for individual blocks were compared post hoc to saline values via paired sample t tests.

Histology

After completion of behavioural testing, animals were sacrificed by exposure to carbon dioxide. The brains were removed and postfixed in 4% paraformaldehyde for at least 24 h. Brains were sectioned coronally on a cryostat or freezing microtome. 30 to 40 μm sections were stained with cresyl violet, and the location of the injector tips was mapped onto standardized sections of the rat brain (Paxinos and Watson 1998).

Results

Histological analysis revealed that all cannulae tips were located within the OFC. A depiction of the locations of cannulae tips is provided in Fig. 2.

Basal levels of impulsive choice

Saline microinfusions did not significantly affect choice patterns when compared to stable post-operative baseline in either the No Cue group (session \times delay: $F_{3, 45} = 1.377$, not significant [NS]) or the Cue group (session \times delay: $F_{3, 45} = 1.805$, NS). Animals in both the No Cue and Cue groups were further divided into low or high impulsive subgroups based on their baseline performance over five stable post-operative sessions (Barbelivien et al. 2008; Perry et al. 2008; Tomie et al. 1998; Winstanley et al. 2003b). Those who chose the large reward lever more than 75% of the time when lever choice was averaged at the 0 s and 15 s delays were labelled as low impulsive (LI), and the remainder of the animals were labelled as high impulsive (HI), resulting in the identification of seven LI and nine HI animals in both the No Cue and Cue groups (Fig. 3). This classification of impulsivity level produced a significant between-subjects effect in the analysis of baseline behaviour in both the No Cue (impulsivity level: $F_{1, 14} = 10.129$, $p < 0.007$) and Cue groups (impulsivity level: $F_{1, 14} = 44.513$, $p < 0.0001$), suggesting that the choice behaviour of these two groups can be meaningfully dissociated.

Choice latency was slightly longer for animals in the No Cue group (0.68 ± 0.07 s, mean \pm SEM) compared to the Cue group (0.57 ± 0.047 s); however, this difference was not statistically significant ($F_{1, 28} = 1.019$, NS). Furthermore, animals classified as HI or LI did not differ in their latency to respond on the levers (all F 's < 1.91 , NS). Omissions remained very low throughout the experiment in all groups and likewise were independent of basal levels of impulsive choice (No Cue: 0.031 ± 0.021 ; Cue: 0.0 ± 0.0 ;

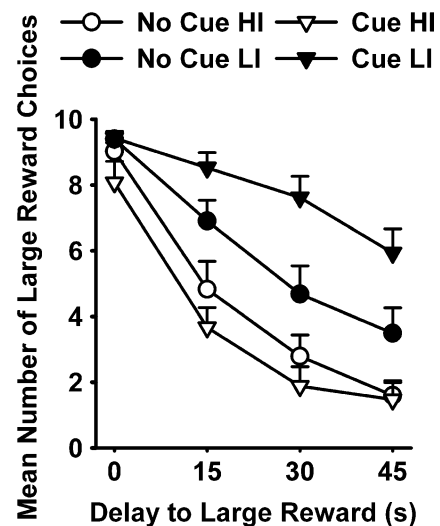


Fig. 3 Baseline levels of impulsive choice. Both high impulsive (HI) and low impulsive (LI) groups of rats are evident in the cue and no cue conditions. Data shown represent the average of five stable post-operative sessions \pm SEM

group: $F_{1, 28}=2.036$, NS; impulsivity level: $F_{1, 28}=0.032$, NS; delay: $F_{3, 84}=0.700$, NS; delay \times group \times impulsivity level: $F_{3, 84}=1.368$, NS).

OFC inactivation by baclofen and muscimol microinfusions

No Cue group Microinfusion of baclofen and muscimol had differential effects depending on animals' baseline level of impulsivity (dose \times impulsivity level: $F_{1, 14}=4.573$, $p<0.05$; Fig. 4). Following OFC inactivation, HI rats chose the larger, delayed reward more frequently, indicating a decrease in impulsive choice that was particularly evident at the longest delay (dose: $F_{1, 8}=9.017$, $p<0.02$; dose \times delay: $F_{3, 24}=3.374$, $p<0.03$). In contrast, the choice behaviour of LI rats remained unchanged (dose: $F_{1, 6}=0.270$, NS; dose \times delay: $F_{3, 18}=0.826$, NS). Neither group showed any changes in the number of omissions (all F 's < 3.4 , NS). However, the latency to respond across all trial blocks was slightly longer in LI animals after inactivation of the OFC (saline 0.52 ± 0.05 s, baclofen + muscimol 0.90 ± 0.10 s; dose: $F_{1, 8}=25.962$, $p<0.002$; dose \times delay: $F_{3, 24}=1.561$, NS). The response latency in

HI rats was unaffected (dose: $F_{1, 8}=3.029$, NS; dose \times delay: $F_{3, 24}=1.754$, NS).

Cue group As in the No Cue group, the effect of OFC inactivation depended on the baseline level of impulsivity (dose \times impulsivity level: $F_{1, 14}=5.269$, $p<0.04$; Fig. 4); however, the opposite pattern of behaviour was observed. Following microinfusions of baclofen and muscimol into the OFC, LI rats tended to decrease their choice of the larger delayed reward, indicating an increase in impulsive choice (dose: $F_{1, 6}=5.106$, $p<0.06$; dose \times delay: $F_{3, 18}=0.598$, NS). In contrast, OFC inactivation did not alter the choice behaviour of HI rats (dose: $F_{1, 8}=1.283$, NS; dose \times delay: $F_{3, 24}=0.772$, NS), and no changes in the number of omissions or response latency were observed in either group (latency dose \times impulsivity level: $F_{1, 14}=1.033$, NS; omissions dose \times impulsivity level: $F_{1, 14}=0.224$, NS).

Intra-OFC infusion of the DA receptor antagonists eticlopride and SCH 23390

No Cue group Microinfusions of either the D₁ or D₂ receptor antagonist did not significantly alter impulsive choice when the delay to the large reward was unsignalled, regardless of the baseline level of impulsivity (eticlopride dose: $F_{3, 18}=0.315$, NS; dose \times delay: $F_{9, 54}=1.008$, NS; dose \times impulsivity level: $F_{3, 18}=0.950$, NS; SCH 23390 dose: $F_{3, 18}=2.407$, NS; dose \times delay: $F_{9, 54}=1.032$, NS; dose \times impulsivity level: $F_{3, 18}=0.103$, NS; Fig. 5). The latency to respond as well as the number of omissions also remained unchanged across treatment conditions (all F 's < 2.1 , NS).

Cue group In contrast, intra-OFC infusion of the D₂ receptor antagonist eticlopride tended to decrease choice of the large reward when the delay to its delivery was signalled by a cue light, with the strongest effect at the middle dose (dose: $F_{3, 18}=3.067$, $p<0.05$; saline vs. 0.3 $\mu\text{g}/\text{side}$: $F_{1, 7}=4.183$, $p<0.08$; Fig. 5). There was also a trend for the highest dose of the D₁ receptor antagonist SCH 23390 to likewise decrease choice of the larger delayed reward (dose: $F_{3, 18}=2.584$, $p<0.08$; saline vs. 1.0 $\mu\text{g}/\text{side}$: $F_{1, 7}=4.215$, $p<0.07$). Visual inspection of the data indicates that the effects of both eticlopride and SCH 23390 were most pronounced in LI rats (Supplemental Figure S1). However, this distinction was not statistically significant, possibly due to a small number of animals in each group (eticlopride dose \times impulsivity level: $F_{3, 18}=1.710$, NS; SCH 23390 dose \times impulsivity level: $F_{3, 18}=0.636$, NS). Similar to findings from the No Cue group, response latency and omissions also remained unchanged (all F 's < 1.4 , NS).

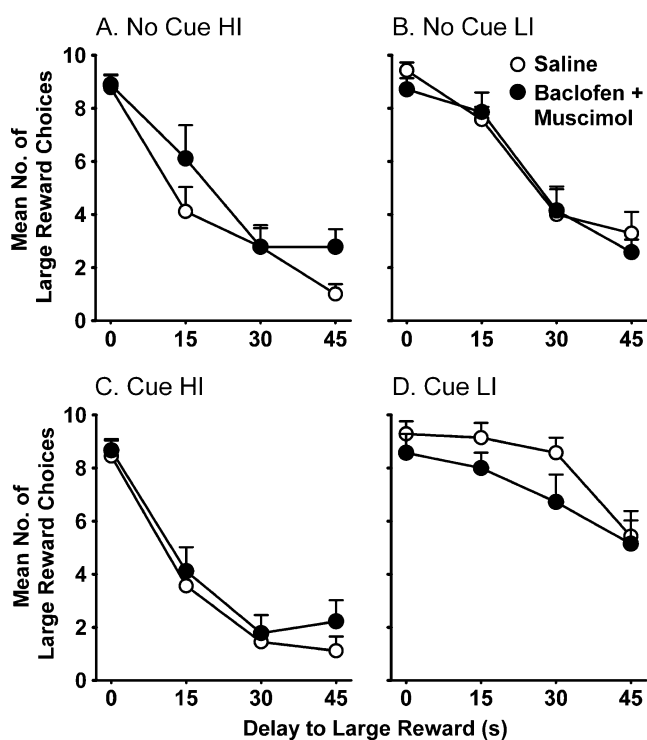
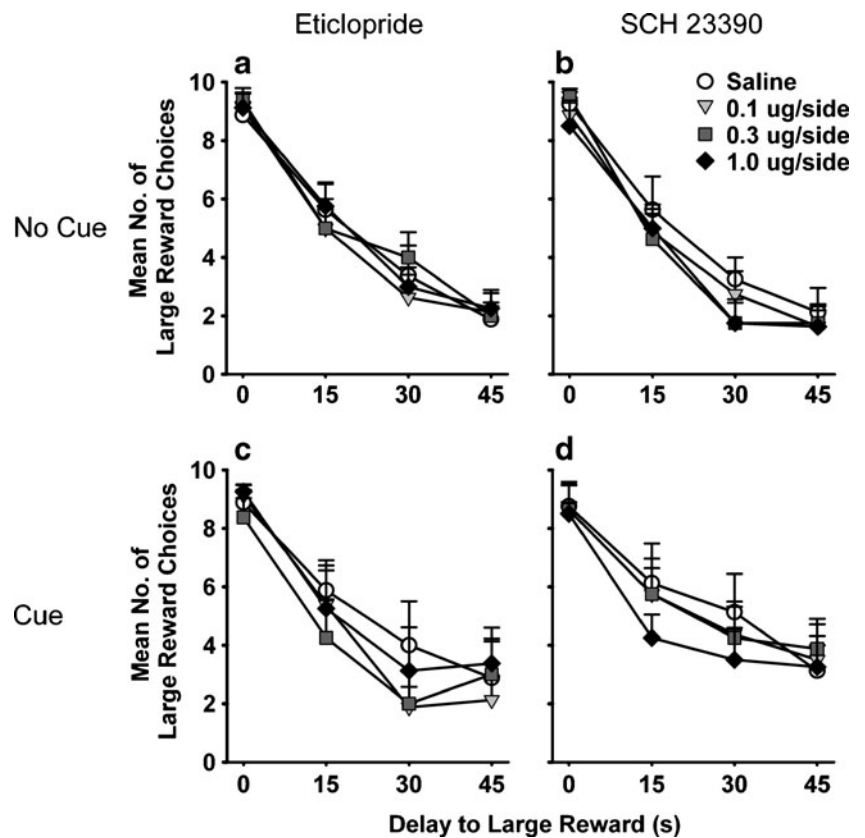


Fig. 4 Effects of baclofen and muscimol infusions on impulsive choice. (a) Animals in the No Cue group showing high levels of impulsive choice then increase in choice of the larger reward upon OFC inactivation, whereas the least impulsive animals in the No Cue group (b) are unaffected. In the Cue group, OFC inactivation fails to alter impulsive choice in highly impulsive animals (c), but decreases choice of the large reward in animals that are less impulsive (d). HI high impulsive, LI low impulsive. Data shown are mean \pm SEM

Fig. 5 Effects of intra-OFC infusion of DA receptor antagonists on choice behaviour. Infusion of either eticlopride (**a**) or SCH 23390 (**b**) fails to alter impulsive choice in the No Cue group. Decreased choice of the large reward is observed in the Cue group after both eticlopride (**c**) and SCH 23390 (**d**) infusions. Data shown are mean \pm SEM



Discussion

Here, we show that signalling the delay to the larger reward facilitates acquisition of a delay-discounting paradigm and has a significant impact on the contribution made by the OFC to delay-discounting judgements. When the delay to the reward was cued, transient inactivation of the OFC increased impulsive choice in animals with a low basal impulsivity level; in contrast, impulsive choice was decreased in the uncued condition in highly impulsive animals. Hence, the effects of OFC inactivation depended on both the presence of a cue during the delay as well as individual differences in basal levels of impulsive choice. Furthermore, intra-OFC infusions of a DA antagonist tended to increase impulsive choice only when a cue was signalling the delay. The presence of such cues may therefore enhance DA transmission within the OFC, which could in turn play a role in mediating preference for the larger delayed reward.

The fact that the level of impulsive decision-making can be affected by cuing the delay-to-reward period may help explain the conflicting results of OFC lesions reported previously (Rudebeck et al. 2006; Winstanley et al. 2004). Subjects were not divided into high or low impulsive subgroups in either of these previous reports, but clear differences in the basal impulsivity levels are evident when

the discounting rates are compared between studies. In the current study, OFC inactivation increased the rate of discounting when a stimulus light was illuminated during the delay, but only when animals already exhibited a low level of impulsive choice. Similarly, using a T-maze apparatus and a fixed delay of 15 s, Rudebeck et al. (2006) observed that animals rarely chose the small immediate reward, and lesions of the OFC likewise increased delay discounting. Although the task did not incorporate an explicit cue such as illumination of a stimulus light, confinement to a small area of the maze during the delay period, further signalled by the raising and lowering of access gates, could have effectively cued the duration of the delay in a comparable fashion. Notably, increased delay discounting following OFC lesions has also been reported using operant-based procedures, when a cue light was used to signal the delay to the larger reward (Mobini et al. 2002).

In contrast to the above-mentioned findings, when the delay-to-reward period was not overtly cued, animals tended to show a comparatively higher baseline level of impulsive choice (i.e. a decreased tolerance for delayed rewards; Cardinal et al. 2000). Under these conditions, OFC lesions have been shown to decrease impulsive choice (Winstanley et al. 2004). In the current study, we likewise found that OFC inactivation decreased choice of the small

immediate reward when the delay was not cued, but this effect was only observed in the most impulsive animals. Hence, it would appear that individual differences in impulsive choice determine whether silencing the OFC leads to increases or decreases in preference for larger delayed rewards, and the functional impact of such baseline differences is critically modulated by signalling of the delay-to-reward period. These data also indicate that the effects of decreasing OFC function on delay-discounting paradigms cannot simply be attributed to increased perseverative responding on the lever favoured at the beginning of the session (see Jones and Mishkin (1972), Rolls et al. (1994), and Chudasama and Robbins (2003) for a discussion of the ability of OFC lesions to increase perseveration), but may instead modify the way in which reward-associated signals influence behavioural choice (Tait and Brown 2007).

Addition of a cue during the delay period provides animals with immediate feedback on their selection, bridging the gap between response and reward delivery. As such, this cue may act as a conditioned reinforcer, facilitating learning of the task by strengthening response–reward associations (Cardinal et al. 2000; Williams and Dunn 1991). Indeed, when the duration of the delay was cued, animals developed stable levels of delay discounting within fewer sessions (22) compared to those tested in the uncued condition (35). Although high and low impulsive subgroups could easily be identified in both cued and uncued conditions, this distinction was most pronounced when a cue was present during the delay, whereas discounting curves of individuals in the No Cue group were more homogeneous. The greater diversity within the Cue group may have arisen through variation in the attribution of incentive salience. Although a conditioned stimulus has the ability to maintain a conditioned response, it does not necessarily act as an effective conditioned reinforcer, despite its ability to successfully predict reward delivery (Robinson and Flagel 2009). The degree to which a conditioned stimulus acquires the properties of an effective conditioned reinforcer may depend on individual differences in the allocation of incentive salience to environmental stimuli (Flagel et al. 2009). Thus, when a cue signalled the delay, animals exhibiting the lowest rate of discounting may have attributed more incentive salience to the cue, and this leads to a higher preference for the larger delayed reward. In contrast, animals showing higher levels of impulsive choice did not register or respond as much to the incentive properties of the cue.

The output from multiple areas within the affective cortico-striatal loop contributes to the decision-making process (Cardinal et al. 2002). It has been suggested that the OFC plays a critical role in maintaining internal representations of a reward's subjective value and updating these value representations in line with changing informa-

tion from the environment (Schoenbaum et al. 2003; Wallis 2007). The results of the present study indicate that the involvement of the OFC in such value assessments may be reflected in individual differences in basal levels of impulsivity. It could be argued that animals that did not show changes in delay-discounting performance following OFC inactivation were less sensitive to the impact of these stimuli when choosing between the two rewards. Thus, the highly impulsive animals in the cue group were less able to use a cue to boost choice of the large reward compared to those displaying lower levels of impulsive choice. Conversely, less impulsive animals in the uncued experiments displayed a reduced aversion to delays imposed before delivery of the large reward. In both instances, animals may not assign as much importance to those environmental stimuli (the cue and the delay, respectively). The output generated by the OFC in these individuals may therefore be less consistent or fundamentally weaker so that its contribution to the decision-making process is reduced, leaving other cortical or subcortical areas to play a greater role in guiding behaviour (see e.g. Cardinal et al. (2001) and Winstanley et al. (2004) for evidence that the nucleus accumbens, medial prefrontal cortex, or basolateral amygdala also mediate delay-discounting performance). Hence, the importance of the OFC in delay discounting may depend, at least in part, on how individuals utilize environmental stimuli in the context of assessing reward value, and this process may affect the basal level of impulsive choice an individual exhibits.

Having considered that animals which were unaffected by OFC inactivation in the current study were less sensitive to environmental stimuli, the converse may be true of animals that did change their choice preference in response to this manipulation. As discussed above, OFC inactivation had significant, albeit opposing, effects on animals that showed either high levels of impulsivity in the uncued paradigm, or low levels of impulsivity when the delay was cued. In the latter group, the presence of the cue meant that the delay had comparatively little impact on the subjective value of the large reward; in the former group, the uncued delay resulted in significantly greater discounting of the large reward. In both cases, the value of the large reward was largely judged based on a secondary characteristic of the reinforcement schedules (the cue and the delay, respectively), and inactivation of the OFC ameliorated these biases in both groups.

Whether this hypothesis turns out to be heuristically useful remains to be determined, but it has been suggested that individual differences in the emphasis placed on reward-paired cues may differentiate individuals vulnerable to drug addiction (Flagel et al. 2009; Tomie et al. 1998). Environmental cues paired with an addictive drug exert inappropriately powerful control over the addicts' behav-

our and make a significant contribution to drug craving and relapse (Goldstein et al. 2009; Kosten et al. 2006; Shaham et al. 2003). Investigating the neurobiological basis of individual differences in the degree to which reward-paired cues dominate behavioural choice may therefore inform our understanding of the relationship between impulsive decision-making and addiction. Experiments aiming to identify possible relationships between the level of impulsive choice and the propensity to self-administer addictive drugs should therefore control for the presence of potential conditioned reinforcers embedded within some delay-discounting schedules.

Although we have shown that signalling the delay is one critical factor affecting the outcome of OFC inactivation on impulsive choice, recent studies indicate that subjective evaluation of the size of the reinforcers may also affect the level of delay discounting observed. By fitting the behavioural output from a sequence of delay-discounting schedules to a multiplicative hyperbolic model, Hø et al. (1999) argue that it is possible to estimate the sensitivity to reward size and to delay, both of which can alter impulsive choice independently. Using this methodology, Kheramin et al. (2002) concluded that the behaviour of OFC-lesioned rats was best approximated by an increase in sensitivity to reward size as well as delay. In these studies, a cue light was used to signal the delay to the large reward and damage to the OFC increased impulsive choice, partially consistent with the findings reported here and elsewhere. However, this effect was reversed if delivery of the small reward was also delayed by a short period. Based on the mathematical modelling of these behavioural data, the authors suggest that delaying the small reward resulted in a marked reduction in its subjective value in OFC-lesioned rats, hence preference increased for the larger delayed reward. However, when only the large reward was delayed, the enhanced sensitivity to delay dominated the decision-making process leading to preference for the small reward. In applying this theory to the data presented here, animals which became less impulsive as a result of OFC inactivation (HI rats in the uncued condition) could have changed their preference largely because the smaller reward was essentially undervalued, whereas the corresponding increase in impulsive choice observed in LI rats in the cued condition arose due to an inability to tolerate the delay to the larger reward.

Whether individual differences in impulsive choice in the cued and uncued version of the task genuinely reflect a differential sensitivity to delay vs. reward magnitude is an interesting question and remains to be empirically determined. However, according to the multiplicative hyperbolic model, the ability of OFC lesions to enhance impulsive choice should be diminished by increasing the value of the larger delayed reward, yet a comparatively greater increase

in choice of the smaller immediate reward following OFC lesions has been observed when the larger delayed reward was ten sugar pellets as compared to the four pellets used here (Rudebeck et al. 2006). One important methodological difference which may explain these inconsistencies is that both the current and latter study reported the effects of silencing the OFC on already established patterns of choice behaviour, whereas Kheramin et al. (2002) lesioned the OFC before the animals learned the delay-discounting task. Whether lesions are performed before or after training can be a critical determinant of the nature of the effects observed. For example, OFC lesions made before animals have learned the relevant Pavlovian and instrumental contingencies do not affect Pavlovian-to-instrumental transfer (PIT). In contrast, if the OFC is lesioned after the contingencies have been learned, yet prior to the PIT test session, then the CS is no longer able to boost levels of instrumental responding (Ostlund and Balleine 2007). As outlined above, other brain areas must subsume control of the decision-making process in the absence of the OFC. Hence, lesions made prior to training indicate the results of activity in such a network independent of contributions from the OFC, whereas lesions made subsequent to learning a task reflect the disruption of a pre-existing balance between OFC output and that of other regions implicated in goal-directed behaviour. A systematic comparison of both manipulations has the potential to provide greater insight into the role of the OFC in reward-related learning and impulse control, and a clear understanding of the methodological approaches used in different experiments will be essential in drawing the most appropriate conclusions.

Previous reports indicate that both systemic and intra-mPFC administration of the D₁ receptor antagonist SCH 23390 can increase impulsive choice in an uncued delay-discounting paradigm, yet systemic administration of the D₂ receptor antagonist eticlopride had no effect (Loos et al. 2010; van Gaalen et al. 2006). In contrast, we observed that intra-OFC infusions of eticlopride increased impulsive choice, and a similar trend was observed for SCH 23390, but these effects were only observed when the delay to the large reward was cued. In considering the basis of these differences, one hypothesis is that decreasing DA transmission specifically within the OFC may diminish preference for the larger delayed reward through reducing the incentive salience of the cue signalling its delivery. In support of this tentative hypothesis, damage to the OFC affects the ability to develop and utilize cue–reward associations, as indicated by deficits in acquisition and performance of Pavlovian autoshaping, or ‘sign-tracking’ (Chudasama and Robbins 2003). The DA system is also thought to be critical in mediating incentive salience, and presentation of cues that have previously been associated with a primary reinforcer

triggers DA release in the mesolimbic system (Berridge and Robinson 1998; Phillips et al. 2003; Schultz et al. 1997). Furthermore, analysis of DA depletion within the OFC using the multiplicative hyperbolic model indicates that the rate of delay discounting is increased, but the subjective valuation of rewards is diminished, paralleling the effects of OFC lesions (Kheramin et al. 2004). The OFC receives dopaminergic input from the ventral tegmental area (VTA), and disconnecting the OFC from the VTA has been shown to disrupt the ability of cues to guide responding for outcomes when the values of those outcomes change (Takahashi et al. 2009). Improving our understanding of how the DA system modulates OFC function, and how this contributes to the expression of impulsive behaviour, may provide valuable insight into both the pathology and treatment of impulse control disorders in which the DA system has been implicated, including ADHD and drug addiction (Volkow et al. 2007; Tripp and Wickens 2009). DA also interacts with other neurotransmitters such as serotonin and noradrenaline, and these interactions may be critical to the manifestation of impulse control disorders (Oades 2008; Arnsten 2009). Future experiments aimed at clarifying the effects of dopaminergic, serotonergic, and noradrenergic agents within the OFC on different forms of impulsive behaviour are clearly warranted.

In summary, the data presented here support the hypothesis that levels of impulsive decision-making can be affected by the influence which reward-related stimuli exert over behaviour (Diergaarde et al. 2009; Flagel et al. 2009). Furthermore, individual differences in impulsive choice, and in sensitivity to such stimuli, may reflect the degree to which the OFC contributes to the decision-making process, and this may be critically modulated by the DA system. Such data may help to explain the divergent effects of OFC manipulations on impulsive choice and strengthen our understanding of OFC dysfunction in psychiatric disorders.

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