Limbic Corticostriatal Systems and Delayed Reinforcement

RUDOLF N. CARDINAL, CATHARINE A. WINSTANLEY, TREVOR W. ROBBINS, AND BARRY J. EVERITT

Department of Experimental Psychology, University of Cambridge, Cambridge, United Kingdom

ABSTRACT: **Impulsive choice, one aspect of impulsivity, is characterized by an abnormally high preference for small, immediate rewards over larger delayed rewards, and can be a feature of adolescence, but also attention-deficit/hyperactivity disorder (ADHD), addiction, and other neuropsychiatric disorders. Both the serotonin and dopamine neuromodulator systems are implicated in impulsivity; manipulations of these systems affect animal models of impulsive choice, though these effects may depend on the receptor subtype and whether or not the reward is signaled. These systems project to limbic cortical and striatal structures shown to be abnormal in animal models of ADHD. Damage to the nucleus accumbens core (AcbC) causes rats to exhibit impulsive choice. These rats are also hyperactive, but are unimpaired in tests of visuospatial attention; they may therefore represent an animal model of the hyperactive–impulsive subtype of ADHD. Lesions to the anterior cingulate or medial prefrontal cortex, two afferents to the AcbC, do not induce impulsive choice, but lesions of the basolateral amygdala do, while lesions to the orbitofrontal cortex have had opposite effects in different tasks measuring impulsive choice. In theory, impulsive choice may emerge as a result of abnormal processing of the magnitude of rewards, or as a result of a deficit in the effects of delayed reinforcement. Recent evidence suggests that AcbC-lesioned rats perceive reward magnitude normally, but exhibit a selective deficit in learning instrumental responses using delayed reinforcement, suggesting that the AcbC is a reinforcement learning system that mediates the effects of delayed rewards.**

KEYWORDS: **delayed reinforcement; impulsivity; impulsive choice; serotonin; dopamine; nucleus accumbens core; anterior cingulate cortex; medial prefrontal cortex; orbitofrontal cortex; basolateral amygdala; attention-deficit/hyperactivity disorder; drug addiction**

INTRODUCTION

Adolescence is a time when people are prone to taking risks and seeking novel experiences. For the majority, this period is navigated safely and much useful experience is gained, but adolescence is a period of disproportionately high morbidity

Address for correspondence: Rudolf N. Cardinal, Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK. Voice: 44-1223-333587; fax: 44-1223-333554.
rudolf.cardinal@pobox.com

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and mortality due to maladaptive behavior[132] (see Refs. 133 and 134). In particular, adolescents may make choices that are rewarding in the very short term, but poor in the longer term. This can be termed impulsive choice. Impulsive choice is one consequence of a failure to learn from or choose appropriately on the basis of delayed reinforcement. This chapter discusses the neurobiological systems that play a part in determining the effects of delayed reinforcement, and that may therefore contribute to impulsivity in adolescence or other pathological states in which impulsive choice features prominently.

Animals act to obtain rewards such as food, shelter, and sex. Sometimes, their actions are rewarded or reinforced immediately, but often this is not the case; to be successful, animals must learn to act on the basis of delayed reinforcement. They may also profit by choosing delayed reinforcers over immediate reinforcers, if the delayed reinforcers are sufficiently large. However, individuals differ in their ability to choose delayed rewards. Self-controlled individuals are strongly influenced by delayed reinforcement and choose large, delayed rewards in preference to small, immediate rewards; in contrast, individuals who are relatively insensitive to delayed reinforcement choose impulsively, preferring the immediate, smaller reward in this situation.[1] Impulsivity has long been recognized as a normal human characteristic[2] and in some circumstances it may be beneficial,[3] but impulsive choice contributes to deleterious states such as drug addiction[4–8] and attention-deficit/hyperactivity disorder (ADHD).[9,10]

Why are some individuals impulsive in their choices? To address these questions, the potential ways in which delayed reinforcement can affect action–outcome *learning* will be considered. Theories of instrumental *choice* involving delayed reinforcement will then be briefly considered. Interventional studies will be reviewed that examine the role of selected neurochemical systems—the serotonin and dopamine neuromodulator systems—and neuroanatomical regions—the nucleus accumbens core (AcbC), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and basolateral amygdala (BLA)—in rats' ability to choose delayed rewards. Finally, the applications of these studies to ADHD and other disorders of impulsivity will be considered.

LEARNING TO RESPOND FOR DELAYED REINFORCEMENT

Instrumental, or operant, conditioning is a procedure in which the experimenter arranges a contingency between an animal's behavior (the operant) and a reinforcing outcome.[11] It creates multiple psychological representations, and therefore delayed reinforcement can affect learning in several ways. Early theorists considered the fundamental problem of delayed reinforcement: how a response can be strengthened by reinforcement that follows it. Hull postulated that the strength of a stimulus–response (S–R) association is inversely related to the delay between the response and the reinforcement.[12] Indeed, instrumental learning has repeatedly been shown to get worse as the response–reinforcer delay is increased.[13–15] An alternative view is that reinforcement never acts "backwards in time" to strengthen past responses; instead, reinforcement always strengthens the response that the animal is presently making. In this scenario, the effects of the delay arise because the longer the time between the response and reinforcement, the more likely it is that the animal has left the be-

havioral state it was in when it responded, so that some other state will be erroneously reinforced.[16–20] Moreover, since Hull's suggestion, it has been shown that when rats respond for reward, they may respond not only via a direct S–R ("habit") association—by which responses are automatically elicited by environmental stimuli as a consequence of the subject's past history of reinforcement—but also via a declarative, goal-directed system, through which the subject is aware of its goals and the actions that will lead to them.[21–24] Finally, learning can be improved if a distinctive environmental cue "bridges" the delay.[15] Such a cue, which reliably precedes delivery of the final reinforcer, can become associated with reinforcement, thereby becoming a conditioned reinforcer with the potential to affect choice on its own. Therefore, there are several systems that might be affected by delays to reinforcement. Subjects may fail to choose a worthwhile reinforcer when it is delayed because a stimulus–response, response–reinforcer, or stimulus–reinforcer association is weaker for the delayed alternative.

CHOOSING BETWEEN REINFORCERS: EFFECTS OF DELAY

Despite this potential complexity, studies of impulsive choice have produced some highly consistent results regarding the effects of delayed reinforcement in

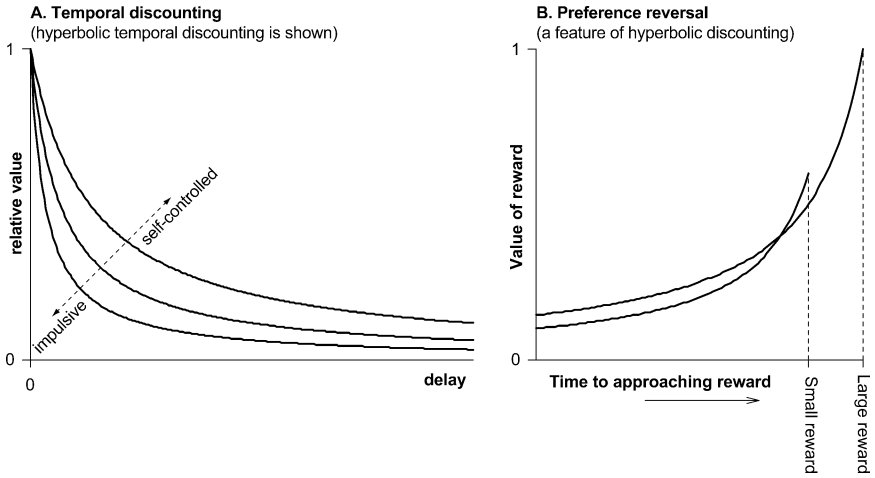

FIGURE 1. (**A**) Humans and other animals value delayed reinforcers less than immediate reinforcers; this is termed temporal discounting. The figure illustrates hyperbolic temporal discounting, governed by the equation $value = magnitude/(1 + K \times delay)$. Large values of K give the steepest curve (the most "impulsive" subjects). (**B**) Preference reversal. Given a choice between an early reward of value 0.6 and a later reward of value 1, hyperbolic discounting predicts that the larger reward will be chosen if the choice is made far in advance (toward the left of the graph). However, as time advances, there comes a time just before delivery of the small reward when preference reverses and the small reward is chosen. Figure adapted from Ainslie.[1]

well-defined choice paradigms. In a typical experimental situation, a subject chooses between an immediate, small reward or a large, delayed reward; the temporal discounting function quantifies the effect of the delay on preference. Early models of choice assumed an exponential model of temporal discounting, so that if V_0 is the value of a reinforcer delivered immediately, then the value of a reinforcer delivered after time t is $V_t = V_0 e^{-kt}$, where k quantifies an individual's tendency to "discount" the future (to value delayed rewards less). The exponential model makes intuitive sense, whether you consider the underlying process to be one in which the subject has a constant probability of "forgetting" its original response per unit time, one in which the "strength" of the response's representation decays to a certain proportion of its previous value at each time step, or one in which the subject behaves as if there is a constant probability of losing the delayed reward per unit of waiting time. Unfortunately, it is wrong; the exponential model has been emphatically rejected by experimental work with humans and other animals. Instead, temporal discounting appears to follow a *hyperbolic* or very similar discount function (FIG. 1A).[15,25–28] One interesting prediction that emerges from hyperbolic (but not exponential) models is that preference between a large and a small reward should be observed to reverse depending on the time that the choice is made (FIG. 1B), and such preference reversal is a reliable experimental finding.[29]

It is not known *why* hyperbolic discounting arises,[30] or what neuropsychological processes are responsible for it. Such discounting might, for example, result from poor knowledge of the contingencies between actions and their outcomes at long delays, or from weak S–R habits, or because subjects are perfectly aware that the delayed reward is available but assign a low value to it.[31] However, given the importance of impulsive choice in addiction[4–8] and ADHD,[9,10] a number of groups have studied the effects on impulsive choice of manipulating neurochemical and neuroanatomical systems implicated in these disorders.

NEUROCHEMICAL STUDIES OF IMPULSIVE CHOICE

Serotonin (5HT)

The suggestion that 5HT is involved in impulse control followed from the twin observations that drugs that suppress 5HT function appear to reduce behavioral inhibition, making animals more impulsive in a "motor" sense,[3,32] and that low levels of 5HT metabolites in cerebrospinal fluid are associated with impulsive aggression and violence in humans[33–36] and risk-taking behavior in monkeys.[37,38] Forebrain 5HT depletion leads to impulsive choice in a variety of paradigms[39–42] and has been suggested to steepen the temporal discounting function, such that delayed rewards lose their capacity to motivate or reinforce behavior.[39,43,44] The 5HT-depleted animal becomes hypersensitive to delays (or hyposensitive to delayed reward). As delayed rewards have unusually low value (utility), the animal consistently chooses small, immediate rewards over large, delayed rewards, a characteristic of impulsivity.[1] Conversely, increasing 5HT function with the 5HT indirect agonist fenfluramine decreases impulsive choice.[45] However, these results are not wholly clear-cut;[46,47] the effects of forebrain 5HT depletion to promote impulsive choice have

sometimes been transient[41] or not observed,[48] and a nonselective 5HT antagonist has been observed to promote self-controlled choice.[49] 5HT may modulate impulsivity in different ways depending on the involvement of different receptor subtypes.[3,46] In humans, lowering 5HT levels via dietary tryptophan depletion[50–52] decreases levels of 5HT metabolites in cerebrospinal fluid,[53,54] an indirect indicator of brain 5HT levels, but although tryptophan depletion may increase "motor" impulsivity,[55] it has not been shown to increase impulsive choice in humans.[56] There are, of course, a number of substantial procedural differences between the tasks commonly used to assess impulsive choice in rats and humans (discussed below in the context of psychostimulants) and it is not presently known by what psychological mechanism 5HT depletion affects impulsive choice in rats.

Dopamine (DA)

Much of the interest in the relationship between DA and impulsivity stems from the discovery that amphetamine and similar psychostimulants are an effective therapy for ADHD.[57] Though these drugs have many actions, they are powerful releasers of DA from storage vesicles in the terminals of dopaminergic neurons, and prevent DA re-uptake from the synaptic cleft, potentiating its action.[58] Sagvolden and Sergeant have proposed that many features of ADHD, including preference for immediate reinforcement and hyperactivity on simple reinforcement schedules, are due to abnormally steep temporal discounting, and that this is due to a hypofunctional nucleus accumbens (Acb) DA system[9,10,59]—though whether ADHD is characterized by a hypodopaminergic or a hyperdopaminergic state, and how this might be "normalized" by psychostimulants, is controversial.[60–63] Many of the inferences regarding the neural abnormalities in children with ADHD have been drawn from studies of the spontaneously hypertensive rat (SHR), an inbred strain of rat that serves as an animal model of ADHD.[64–67] This rat exhibits pervasive hyperactivity and attention problems that resemble ADHD, exhibits a steeper "scallop" of responding on fixed-interval schedules of reinforcement (which can be interpreted as abnormally high sensitivity to immediate reinforcement),[65] is impulsive on measures of "execution impulsivity,"[68] and has a complex pattern of abnormalities in its DA system.[69–75]

Impulsive choice may reflect a lack of effectiveness of delayed reinforcement, and has been suggested to underlie ADHD, or at least subtypes of ADHD.[9,10,76,77] ADHD is amenable to treatment with psychomotor stimulant drugs,[57,78] suggesting that they might promote the choice of delayed rewards. In fact, the effects of acute administration of psychostimulants on laboratory models of impulsive choice have varied. Some studies have found that they promote choice of delayed reinforcers,[65,79–82] while others have found the opposite effect.[49,83,84] Indeed, the same psychostimulant can have opposite effects in different tasks designed to measure impulsivity. [82] These differences may reflect several factors. One is the presence of cues or signals present during the delay. Providing a signal during a delay to reinforcement generally increases the rate of responding during the delay in free-operant tasks,[85] and can promote choice of the delayed reinforcer.[86] One reason for this may be that the signal becomes associated with the reinforcer and acquires conditioned reinforcing properties of its own; these can affect choice.[87] We tested the effects of amphetamine on a discrete-trial task in which rats were offered the choice of a small,

immediate reinforcer or a large, delayed reinforcer (FIG. 2), and found that amphetamine promoted choice of the small, immediate reinforcer if the large, delayed reinforcer was not signaled, but promoted choice of the large, delayed reinforcer if it was signaled.[88] This may be because amphetamine increases the effects of conditioned reinforcers,[89–92] which in this situation would tend to promote choice of the delayed reinforcer. This signal- or cue-dependent effect of amphetamine can explain some of the past discrepancies in the literature.[49,79,80,82] However, conditioned reinforcement is certainly not the only procedural difference between studies that have found differing effects of psychostimulants. Perhaps the most obvious difference between studies of human impulsive choice and animal models is that humans can be offered explicit choices (hypothetical or real) without prior experience of the situation[81,93,94]—"prepackaged" action–outcome contingencies. Other animals must learn these contingencies through experience, implying that the whole gamut of psychological representations that contribute to their actions (including goal-directed actions, S–R habits, and conditioned reinforcers) can influence their choices, and potentially be influenced by psychostimulants.

It should also be emphasized that few studies of the effects of psychostimulants on impulsive choice have addressed the pharmacological basis of their effects. However, Wade *et al.*[80] have shown that mixed or D2-type DA receptor antagonists induce impulsive choice, while D1-type receptor antagonists do not, suggesting that D2 DA receptors normally promote choice of delayed reinforcement, while Winstanley *et al.* have recently found that amphetamine appears to affect choice through 5HT as well as DA neurotransmission.[48]

NEUROANATOMICAL STUDIES OF IMPULSIVE CHOICE

In contrast to the literature on the neurochemistry of impulsivity, research into the neuroanatomical basis of impulsive choice is a young field. We began our studies in this area by considering the role of three candidate structures that may be involved in regulating choice between alternative reinforcers, namely the AcbC and two of its cortical afferents, the ACC and mPFC. These structures are firmly implicated in reinforcement processes: the Acb is a key site for the motivational impact of impending rewards[23,95–98] and many of its afferents are involved in reward-related learning, including the ACC[99–101] and mPFC.[102–105] These regions are also important recipients of dopaminergic and serotonergic afferents.[106,107] Additionally, abnormalities of all three regions have been detected in humans with ADHD and in animal models of ADHD. Abnormal functioning of prefrontal cortical regions, including the mPFC and ACC, has been observed in ADHD patients.[108–110] In the SHR, differences in DA receptor density and gene expression have been observed within the core and shell regions of the Acb,[73–75, 111] while abnormalities of DA release have been detected in the Acb[69–71] and prefrontal cortex,[72] in addition to possible dysfunction in the dorsal striatum and amygdala.[72,112]

Nucleus Accumbens (Acb)

We used the task described earlier (FIG. 2) to examine the effects of excitotoxic lesions of the nucleus accumbens core (AcbC) on rats' ability to choose a delayed

reward.[113] No cues were present during the delay, to avoid any potential confounds arising from conditioned reinforcement effects, and subjects were trained preoperatively, assigned to matched groups, operated upon, and retested postoperatively, to avoid any possible effects of the lesion on learning of the task. AcbC-lesioned subjects were rendered impulsive in their choices: they exhibited a profound deficit in their ability to choose a delayed reward, and persisted in choosing impulsively even though they were made to experience the larger, delayed alternative at regular intervals. This effect was not due to an inflexible bias away from the lever producing the delayed reinforcer: AcbC-lesioned rats still chose the large reinforcer more frequent-

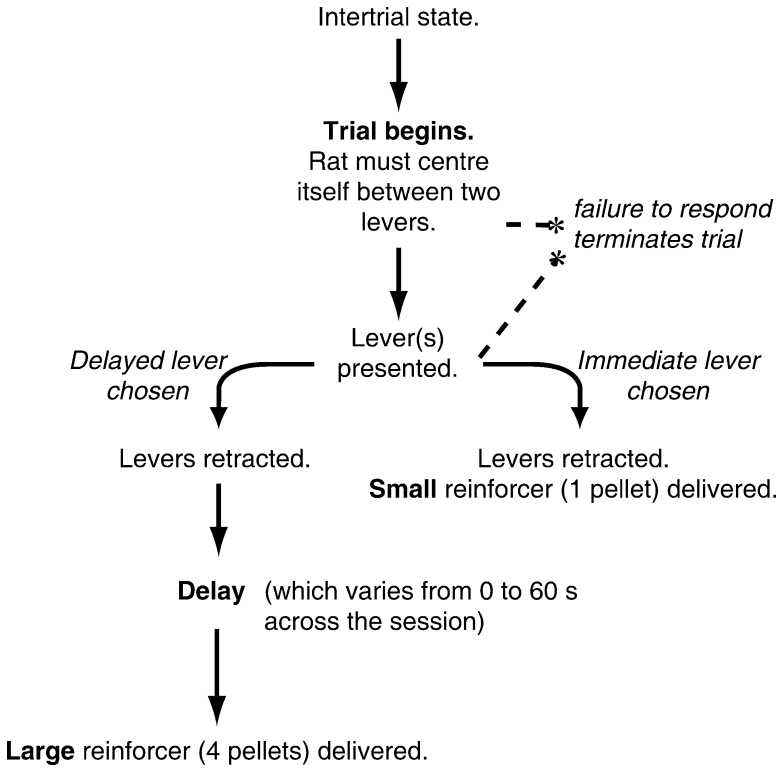

FIGURE 2. Delayed-reinforcement choice task[88,113] based on the work of Evenden and Ryan.[49] Hungry rats regularly choose between two levers. Responding on one lever leads to the immediate delivery of a small food reward (1 pellet); responding on the other leads to a much larger food reward (4 pellets), but this reward is delayed for between 0 and 60 seconds. The figure shows the format of a single trial; trials begin at regular intervals (every 100 s), so choice of the small reinforcer is always suboptimal. Sessions consist of 5 blocks. In each block, two single-lever trials are given (one trial for each lever), to ensure the animals sample the options available at that time; these are followed by ten choice trials. The delay to the large reinforcer is varied systematically across the session: delays for each block are 0, 10, 20, 40, and 60 s, respectively. In the so-called "signaled" or "cue" condition, a stimulus light is illuminated during the delay to the large reinforcer; this is absent in the "unsignaled" or "no cue" condition.

ly at zero delay than at other delays, and removal of the delays resulted in a rapid and significant increase in the rats' preference for the large reinforcer. Although a few lesioned subjects avoided the large reinforcer alternative postoperatively even when the delay was zero, this was probably due to within-session generalization from trial blocks at which delays were present (see FIG. 2). Prolonged training in the absence of delays restored a near-absolute preference for the large reinforcer in the majority of subjects—who were then much more impulsive than shams again when delays were reintroduced.[31] These results indicate that AcbC-lesioned rats are able to discriminate the two reinforcers, but prefer immediate small rewards to larger delayed rewards.

This task involves choice between reinforcers that differed in both magnitude and delay. Therefore, impulsive choice might arise as a result either of altered sensitivity to reinforcer magnitude, or delay, or both.[43] Lesioned rats might have chosen the immediate small reward because they did not perceive the large reward to be as large (relative to the small reward) as sham-operated controls did, in which case the abnormally low magnitude of the large reward would be insufficient to offset the normal effects of the delay. Alternatively, they might have perceived the reward magnitudes normally, but were hypersensitive to the delay. The latter explanation—hypersensitivity to the effects of the delay—appears more likely. AcbC-lesioned rats preferred the larger reward to the smaller,[31,113] and rats with excitotoxic lesions of the whole Acb [114, 115] or of the AcbC (Cardinal and Cheung, unpublished data) appear just as sensitive to the magnitude of reward as normal rats. Acb lesions have also produced delay-dependent impairments in a delayed-matching-to-position task.[116]

If this interpretation is correct, and AcbC lesions induce hypersensitivity to delays of reinforcement, then the effects of AcbC lesions might also extend to *learning* with delayed reinforcement, as well as choice involving delayed reinforcers. In order to learn which actions are the correct ones that eventually lead to reinforcement, some mechanism must "bridge" the delay between action and outcome. We recently examined the ability of AcbC-lesioned rats to learn a free-operant response task (FIG. 3) in which every lever press produced a food pellet, but this reinforcement was delayed by 0, 10, or 20 s in different groups. Increasing delays impaired learning in normal rats to some degree, which is a well-known finding.[13–15] Rats with AcbC lesions were unimpaired (compared to sham-operated controls) when there was no delay, but were profoundly impaired when there was a delay between action and outcome, compared to shams learning with the same delay (Cardinal and Cheung, unpublished data).

Taken together, these results suggest that the AcbC is a structure specialized for the difficult task of learning with, and choosing, delayed reinforcement. Further understanding of the mechanism by which it does so, or sometimes fails to do so, would provide insight into the pathology of a number of neuropsychiatric disorders. Given the involvement of the Acb in aversive motivation,[117,118] it will also be important to determine whether lesions of Acb induce impulsive choice in an aversive context, impairing the ability to choose a small immediate penalty in preference to a large delayed penalty.

Major glutamatergic afferents to the AcbC arrive from the ACC, mPFC, OFC, and BLA; the contribution of these structures to choice between delayed reinforcers will be considered next.

Anterior Cingulate Cortex (ACC)

Excitotoxic lesions of the ACC had no effect in this delayed-reinforcement choice task,[113] showing that the ACC is not required for rats to choose a delayed reinforcer. This finding stands in apparent contrast to previous reports of motor impulsivity or disinhibited responding in ACC-lesioned rats. For example, such rats have been found to overrespond to unrewarded stimuli,[100,101] and to respond prematurely in situations where they are required to wait.[119] However, motor ("execution") impulsivity and impulsive choice ("outcome impulsivity") are known to be dissociable.[3] Thus, these results suggest that despite findings of ACC abnormalities in disorders of impulsivity,[109,110] ACC dysfunction is not an important contributor to impulsive choice.

In the delayed-reinforcement choice task (FIG. 2),[113] subjects choose between reinforcers that differ in magnitude and delay (small immediate versus large delayed) but do not differ in probability (both are delivered with probability 1) or response effort (both require a single lever press). However, Walton *et al.*[120] found that large mPFC lesions encompassing prelimbic cortex (PrL), infralimbic cortex (IL), and ACC altered rats' preference when the two alternatives differed in magnitude, response effort, and delay (although delay was not controlled directly). Subjects were offered the choice of running down a short alley to obtain two pellets, or climbing over a 30-cm-high barrier to obtain four pellets. Large mPFC lesions substantially

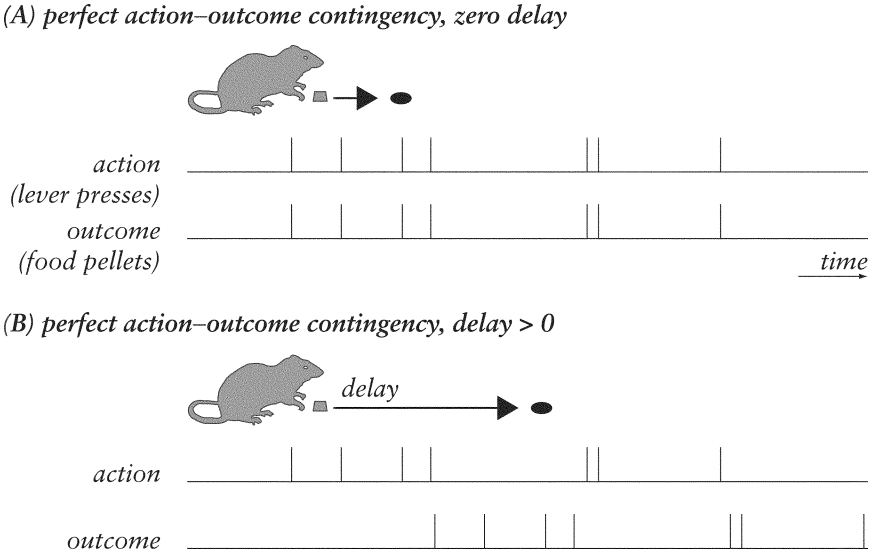

FIGURE 3. Free-operant learning with delayed reinforcement. When an animal is free to perform an action (operant) to obtain a rewarding outcome, it readily learns to do so if the action–outcome contingency (the increase in the likelihood of obtaining the outcome that is produced by performing the action) is good and if there is no delay between action and outcome (**A**). Even with a perfect action–outcome contingency, learning is impaired by imposing delays between the action and the outcome (**B**), yet animals do succeed in this task.

increased rats' preference for the small-reward, low-effort alternative. Nevertheless, lesioned subjects were capable of surmounting the obstacle if there was no low-effort alternative, and their decisions were flexible in that they responded to alterations in either the cost (effort) or the benefit of the alternatives. This effect has since been localized to the ACC: selective ACC lesions impaired performance but PrL/IL lesions had no effect on this task.[121] One interpretation of these results is that the ACC is involved in the assessment of response effort but not the delay to reinforcement.

Medial Prefrontal Cortex (mPFC)

Lesions of the mPFC (primarily PrL and IL) "flattened" the within-session shift from the large to the small reward exhibited by rats performing the delayed-reinforcement choice task shown in FIGURE 2.[113] That is, their preference for the large reward was *below* that of shams at zero delay, but *above* that of shams at the maximum delay—a regression toward indifference—although they responded appropriately when the delays were removed, preferring the larger reinforcer. There is no obvious explanation for this effect within theories of choice of delayed reinforcement, implying that the mPFC lesion resulted in some form of insensitivity to the contingencies or stimuli present in the task. One possibility is that mPFC lesions disrupted the control over behavior by the passage of time in each session. There is strong evidence that normal rats learn a session-wide temporal discrimination in this task, and that this temporal discriminative stimulus comes to control responding—in particular, the tendency to shift from the large to the small reward as the session progresses.[88] Disruption of such temporal stimulus control might be expected to produce a "flattening" of the within-session shift of the kind seen in mPFC-lesioned rats. Indeed, aspirative lesions of the mPFC have previously been shown to induce a deficit in timing ability in rats;[122] lesioned subjects showed impaired temporal discrimination in the peak procedure, an operant task that assesses the ability to time a discriminative stimulus.[123,124] Consistent with the view that mPFC lesions did not affect the basic process of choosing between reinforcers of different value in this task, combined PrL/IL lesions did not affect choice between small/low-effort and large/high-effort alternatives in the task of Walton *et al.*[121]

Orbitofrontal Cortex (OFC)

The OFC is a prefrontal cortical region that projects to the AcbC and is strongly implicated in the assessment of reward value. Mobini *et al.*[125] recently found that lesions encompassing the OFC induced impulsive choice in a task very similar to that described previously. As before, results from this task do not indicate whether the impulsive choice was as a result of altered sensitivity to reinforcer magnitude or delay. Although these lesions damaged PrL in addition to the OFC,[125] the hypothesis that OFC damage was responsible for the behavioral effect is strengthened by the finding that mPFC lesions encompassing PrL do not induce impulsive choice.[113] In contrast, Winstanley *et al.*[135] recently found that OFC lesions induced the opposite effect—better self-control than shams—in exactly the paradigm described previously.[113] This apparent discrepancy requires explanation. One possible reason is that subjects in the Winstanley *et al.* study were trained before the OFC was destroyed and retested postoperatively, while Mobini *et al.* trained and tested postoperatively.

Another is that Mobini *et al.* offered rats a choice between a 1-pellet immediate reinforcer and a 2-pellet delayed reinforcer, whereas Winstanley *et al.* used a 1-pellet immediate reinforcer and a 4-pellet delayed reinforcer. Differences in subjects' sensitivity to either the delay or the magnitude of reinforcement can play a role in determining preference in this task[31,43,125] and it may be that OFC lesions affect both[125]—a hypothesis for which Kheramin *et al.*[126] have found direct support. This emphasizes the necessity for quantitative analysis of delay and magnitude sensitivity[43] or the use of multiple, very different paradigms to provide independent measurements of sensitivity to delay and magnitude.[31]

Basolateral Amygdala (BLA)

Finally, Winstanley *et al.*[135] have recently found that excitotoxic lesions of the BLA promote impulsive choice in the delayed-reinforcement choice task shown in FIGURE 2. This suggests that a network including the BLA, OFC, and AcbC is involved in regulating choice between reinforcers differing in magnitude and delay; the BLA and OFC are extensively interconnected and both project to the AcbC. However, the precise manner in which the three structures interact in a choice situation is far from clear; the observations that BLA and OFC lesions can have opposite effects in exactly the same paradigm (Winstanley *et al.*[135]), and that OFC lesions can have effects on multiple aspects of reinforcer assessment,[126] suggest that any such interaction is likely to be complex.

CONCLUSIONS

The integrity of the Acb is critical for animals to tolerate delays to appetitive reinforcement.[113] This observation provides information on the neural systems through which delayed reinforcement normally affects behavior, but the observation that AcbC damage can induce impulsive choice also has implications for the understanding of ADHD and drug addiction, two clinical disorders in which impulsive choice is a factor, and potentially for impulsivity in adolesecnce. In addition to being impulsive, AcbC-lesioned rats are also hyperactive,[113,127] but they do not appear to be inattentive.[128,129] Destruction of the AcbC does not, therefore, mimic all the signs of ADHD, but these findings suggest that the behavior of rats with AcbC damage resembles that of humans with the hyperactive–impulsive subtype of ADHD.[130] The adolescent nucleus accumbens differs both in dopamine function and synaptic plasticity from that of the adult (see, e.g., Refs. 136–138), though whether any such differences contribute to impulsive behavior in adolescence[139] is at present unknown.

The same considerations apply to drug addiction, in which impulsive choice plays a prominent role in maintaining the selection of drugs of abuse in favor of other, longer-term rewards.[4–8] Drugs of abuse (including opiates, ethanol, and psychostimulants) can produce chronic neuroadaptations in brain regions including the Acb,[131] and chronic methamphetamine has been shown to increase impulsive choice in rats.[79] One mechanism contributing to addiction may therefore be the ability of drugs of abuse to induce damage or dysfunction in the AcbC, further promoting subsequent impulsive choice and future drug taking.

Impulsive choice may also be produced by damage to the BLA (Winstanley *et al.*[135]) or OFC,[125] two prominent afferents to the AcbC, though the exact contribution of these structures may be complex[126,135] and the manner in which they interact with each other and with the AcbC to determine an animal's preference among different reinforcers is not yet clear.

Interventional neuroanatomical studies of impulsive choice are clearly important for the understanding of the pathogenesis of ADHD, for they allow a causal role to be established between dysfunction of a brain region and impulsive choice. This may make it possible to distinguish the brain regions that underlie different types of impulsivity,[3] and to segregate the neural abnormalities that contribute to complex disorders such as ADHD and drug addiction and to the normal variation in impulsive behavior during adolescence. Although the ACC and mPFC have been shown to be abnormal in disorders of impulsivity,[108–110] damage to these regions does not produce impulsive choice in rats.[113] The abnormalities of structure or function observed in these regions in ADHD brains may therefore be responsible for other features of the disorder (such as inattention or motoric disinhibition),[119] or these regions may have altered as a consequence of a disease process beginning elsewhere. A clearer understanding of the neurochemical and neuroanatomical basis of disorders of impulsive choice may lead to more effective therapy.

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