Impulsive Choice Induced in Rats by Lesions of the Nucleus Accumbens Core

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Impulsive choice is exemplified by choosing a small or poor reward that is available immediately, in preference to a larger but delayed reward. Impulsive choice contributes to drug addiction, attention-deficit/hyperactivity disorder, mania, and personality disorders, but its neuroanatomical basis is unclear. Here, we show that selective lesions of the nucleus accumbens core induce persistent impulsive choice in rats. In contrast, damage to two of its afferents, the anterior cingulate cortex and medial prefrontal cortex, had no effect on this capacity. Thus, dysfunction of the nucleus accumbens core may be a key element in the neuropathology of impulsivity.

When animals act to obtain reinforcement, there is always some delay between the action and its outcome; thus, to control the world successfully, animals must be able to use delayed reinforcement. This ability shows individual variation: Impulsive individuals are influenced less by delayed reinforcers than are self-controlled individuals (*1–4*). The neural mechanism by which delayed reinforcement affects behavior is not currently understood, but several lines of evidence suggest the nucleus accumbens (Acb) and its cortical afferents, including the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC), as candidate structures that may be involved in regulating choice between alternative reinforcers. First, these structures have been implicated in reinforcement processes: The Acb is a key site for the motivational impact of impending reinforcers (*5, 6*), and its cortical afferents (including the ACC and mPFC) are also involved in reinforcement learning (*7–9*). Second, these structures are regulated by major dopaminergic and serotonergic afferents, and pharmacological manipulations of these systems affect impulsive choice in rats (*2, 10–13*). Third, abnormalities of limbic circuits have been detected in impulsive individuals. Abnormal function of the mPFC and ACC has been observed in humans with attention-deficit/hyperactivity disorder (ADHD) (*14–16*), whereas the spontaneously hypertensive rat (SHR), widely used as an animal model of ADHD (*3*), exhibits abnormalities of dopamine release in the Acb and prefrontal cortex (*17*) and differences in dopamine receptor density and gene expression within the Acb (*18*).

The present study investigated the effects of lesions of the nucleus accumbens core (AcbC), ACC, or mPFC on rats' capacity to choose a delayed reinforcer. Evenden and Ryan (*19*) developed a model of impulsive choice in which food-restricted rats choose between a small, immediate appetitive reinforcer and a large, delayed reinforcer in discrete trials; the delay to the large reinforcer is increased in steps as the session progresses. We trained rats on this task (Fig. 1) and assigned them to matched groups (*20*); they were then randomly assigned to receive excitotoxic lesions or sham lesions of the AcbC, ACC, or mPFC (*21*) before being retested (*22–24*). Before surgery, rats exhibited a within-session shift in preference from the large to the small reinforcer as the large reinforcer was progressively delayed (Fig. 2, A to C), as is typical for trained subjects performing this task (*13, 19*).

Lesions of the AcbC induced a profound and lasting deficit in rats' ability to choose the delayed reinforcer; they made impulsive choices (Fig. 2D). This was not due to an inflexible bias away from the lever producing the delayed reinforcer: AcbC-lesioned rats still chose the large reinforcer more frequently at zero delay than at other delays, and removal of the delays resulted in a rapid increase in the rats' preference for the large reinforcer (Fig. 2G). Thus, the pattern of choice clearly reflected a reduced preference for the large reinforcer when it was delayed. This suggests that delays reduced the effectiveness or value of reinforcers much more in AcbC-lesioned rats than in sham-operated controls.

AcbC-lesioned rats were hyperactive and slower to habituate to the novel environment of the locomotor testing apparatus, as described previously (*25*). They were also ~10% lighter than controls ($P < 0.01$ throughout testing). However, it is unlikely that differences in primary motivation contributed to the impulsive choice of these rats. First, although they ate their maintenance diet more slowly than did controls, they did not differ in consumption of the sucrose reinforcer used. Second, manipulation of motivational state does not affect choice on this task (*13*). Third, the performance of AcbC-lesioned rats was not comparable in other respects to that of sated rats (*13*); for example, they did not fail to respond more often than did controls. Finally, it has been shown (*26*) that Acb-lesioned rats remain sensitive to reinforcement magnitude and can work for primary reinforcement for long periods when no alternative is available.

In the present study, AcbC-lesioned rats also exhibited discrimination between the large and small reinforcers. Although these rats initially preferred the small reinforcer at zero delay, this paradoxical finding probably reflects an induced bias away from the lever providing delayed reinforcement (*13, 19*). Prolonged retraining with zero delay resulted in 50% of lesioned rats and 70% of controls exhibiting ≥90% preference for the large reinforcer in all trial blocks. Nevertheless, these lesioned rats remained hypersensitive to delays when they were reintroduced: Their preference for the small immediate reinforcer

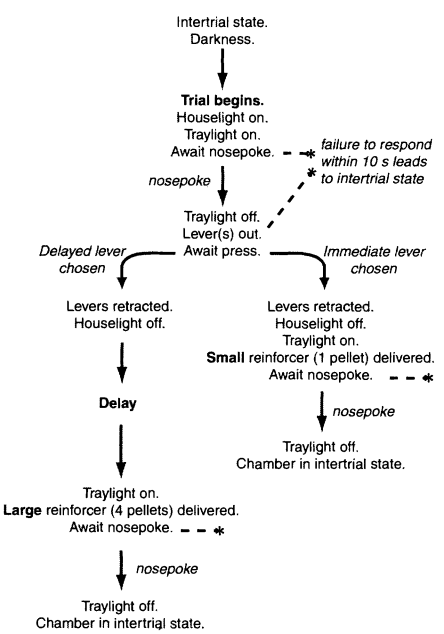

Fig. 1. Delayed reinforcement choice task. The format of a single trial is shown; trials began at 100-s intervals. A session lasted 100 min and consisted of five blocks, each comprising two trials in which only one lever was presented (one trial for each lever, in randomized order) followed by 10 choice trials. The delay to the large reinforcer was varied systematically across the session. Delays for each block were 0, 10, 20, 40, and 60 s, respectively.

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was significantly higher than that of controls ($P < 0.05$), showing that impulsivity was present even when reinforcement discrimination was equivalent at zero delay.

AcbC-lesioned animals exhibited at least two signs of ADHD (*3, 4*): locomotor hyperactivity and impulsive choice. However, attentional deficits are not evident in such animals: Neither 6-hydroxydopamine (6-OHDA)–induced dopamine depletion of the Acb (*27*) nor excitotoxic lesions of the AcbC (*28*) affect accuracy in tests of visuospatial attentional function. Thus, AcbC-lesioned rats may represent an animal model of the hyperactive-impulsive subtype of ADHD (*4*).

Our results show that the integrity of the Acb is critical for animals to tolerate delays to appetitive reinforcement. The possibility that the AcbC is required to maintain the value of a reinforcer over a delay may provide a novel insight into Acb function. Neuronal activity in the primate ventral striatum is related to the expectation of reinforcement across a delay; such activity is a candidate representation of the goals of behavior (*29*). Striatal neurons also respond to past events, maintaining a form of memory that might assist the association of past acts with reinforcement (*29*). These findings are the basis for computational models of striatal function (*30*) and indicate the nature of the information that the AcbC may use to promote actions leading to delayed reinforcement. Additionally, our results demonstrate a role for the Acb in action selection even when those actions do not differ in response effort or cost. Thus, reduced preference for delayed reinforcement may explain the observation that Acb dopamine depletion prevents rats from working hard for a preferred food (*31*) and impairs responding on high-effort schedules (*32*), because such schedules also impose delays to reinforcement.

Lesions of the ACC, by contrast, did not affect the rats' ability to choose a delayed reinforcer; their pattern of choice was indistinguishable from that of controls (Fig. 2E) and remained sensitive to unexpected removal of the delays (Fig. 2H). This finding contrasts with previous reports of disinhibited responding in ACC-lesioned rats. For example, such rats have been found to overrespond to unrewarded stimuli (*7*) and to respond prematurely in situations where they are required to wait (*33*). However, a dissociation between motor impulsivity and impulsive choice is not unprecedented (*2*).

In the mPFC-lesioned group, preference for the large reinforcer was below that of controls at zero delay, but above that of controls at the maximum delay (Fig. 2F). However, a shift from large to small reinforcer (albeit small) persisted in lesioned rats (Fig. 2F), and they remained sensitive to removal of the delays (Fig. 2I). A plausible interpretation is that mPFC lesions disrupted the control over behavior by the passage of time in each session, consistent with the effects of aspirative mPFC lesions on timing (*34*).

Thus, lesions of the AcbC induced impulsive choice, whereas lesions of two of its cortical afferents did not. An important task for further investigation is to specify which afferents to the AcbC contribute to its ability to promote the choice of delayed reinforcers. One obvious candidate that may convey information concerning reinforcer value to the Acb is the basolateral amygdala (*6*). Another is the orbitofrontal cortex (OFC), also implicated in the assessment of reinforcer value and probability (*35*). The OFC may also be an important efferent target of information traveling through the Acb, because this "limbic loop" of the basal ganglia projects back (through the ventral pallidum) to the medial OFC (*36*) and the OFC also exhibits activity reflecting the expectation of reinforcement (*29*).

Our results provide direct evidence that the Acb is involved in the pathogenesis of impulsive choice. In addition to providing neuroanatomical insight into the normal process through which delayed reinforcement affects behavior, and demonstrating a previously unknown function of the Acb, this finding suggests a mechanism by which Acb dysfunction may contribute to addiction, ADHD, and other impulse control disorders.

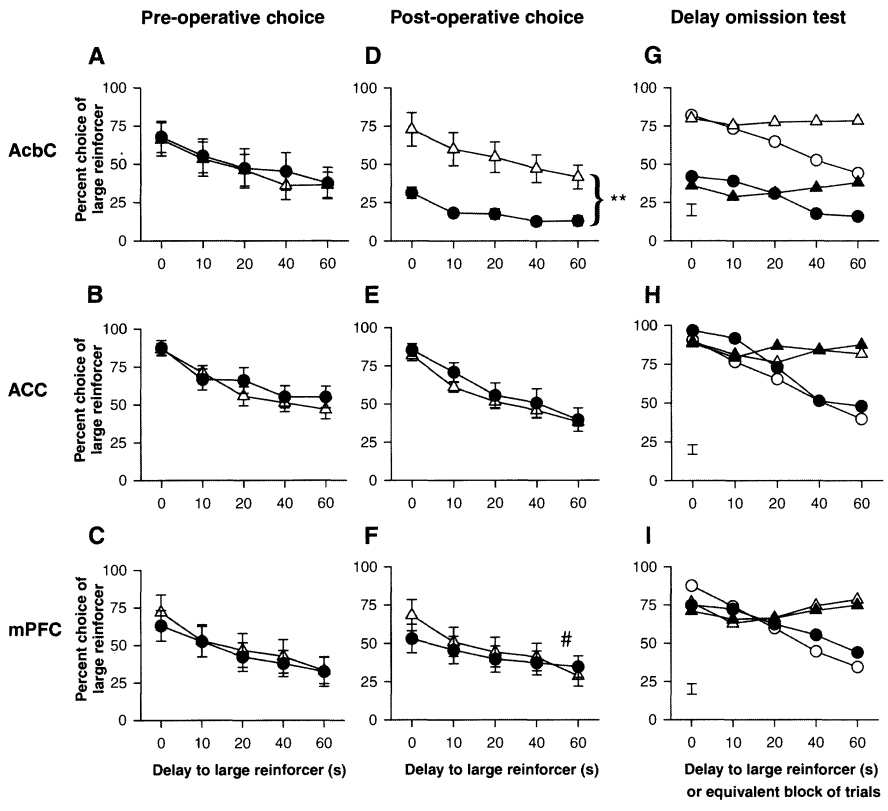

Fig. 2. Effect of lesions of the AcbC (top), ACC (middle), or mPFC (bottom) on choice of delayed reward (●, lesioned group; △, corresponding sham-operated control group). (**A** to **C**) Pattern of choice in the last three sessions preceding surgery; corresponding sham/lesion groups were matched for performance. Rats' preference for the large reinforcer declined with delay ($P < 0.001$, ANOVA). (**D** to **F**) Choice in the first seven postoperative sessions. In (D), the AcbC-lesioned group was markedly impaired (**$F_{1,18} = 13.9$, $P = 0.002$), choosing the delayed reinforcer significantly less often than did controls at every delay, including zero ($P < 0.023$). However, both groups still exhibited a within-session shift in preference (control, $F_{4,36} = 23.7$, $P < 0.001$; AcbC, $F_{4,36} = 14.6$, $P < 0.001$). In (E), ACC lesions had no effect on choice (*F*s < 1, not significant). In (F), the mPFC-lesioned rats exhibited a "flatter" within-session preference shift than did controls (#$F_{3,55} = 3.19$, $P = 0.032$, group × delay interaction; effect of delay in the control group: $F_{3,25} = 17.5$, $P < 0.001$; in the mPFC group: $F_{4,40} = 8.87$, $P < 0.001$). (**G** to **I**) Effects of omitting all delays in alternating sessions (●/○, lesioned/sham groups with delays; ▲/△, lesioned/sham groups without delays; error bars, SED for the three-way interaction). All groups remained sensitive to the contingencies. In (G), delay removal increased both the sham- and core-lesioned groups' preference for the larger reward (sham, $F_{4,36} = 13.7$, $P < 0.001$; AcbC, $F_{1,13} = 5.72$, $P = 0.025$). In (H) and (I), ACC- and mPFC-lesioned rats were as sensitive to removal of the delays as were controls (*F*s < 1.7, not significant).

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20. Seventy-two naïve hooded Lister rats were housed under a reversed light-dark cycle and maintained at 90% of their free-feeding mass. All experimental procedures were subject to UK Home Office approval (Project Licence PPL 80/1324). To avoid the potential effects of the lesions on learning, we trained rats on the task preoperatively and then matched them to groups for surgery. The apparatus, training procedure, and task have been described elsewhere (*13*). Rats were trained and tested in chambers equipped with a 2.8-W houselight and two retractable levers on either side of a food alcove (fitted with a traylight LED) into which 45-mg sucrose pellets could be delivered. Rats were trained to respond for pellets on each lever under a schedule in which every lever-press delivered a pellet. Next, they were trained to make a nosepoke response in the alcove to gain access to a single lever, as described (*13*). Rats were then trained on the delay-of-reinforcement task (Fig. 1) with one session per day. Squads of 24 rats were trained for 19 sessions and then assigned to matched sham/lesion groups by ranking them according to a measure of their sensitivity to delay: the linear regression of percentage of choice of the large reinforcer versus log(delay + 1 s), calculated using data from the last three sessions. The ranked list was divided into pairs, and from each pair one rat was randomly assigned to the sham group and one to the lesion group. Group numbers at this point were 12 (ACC), 12 (ACC sham), 14 (AcbC), 10 (AcbC sham), 14 (mPFC), and 10 (mPFC sham).
21. Animals were anesthetized with Avertin and received excitotoxic lesions of the AcbC [anteroposterior (AP), mediolateral (ML), and dorsoventral (DV) coordinates: AP +1.2, ML ±1.8, DV –7.1 from bregma, 0.5 μl per site], ACC (AP +1.2, ML ± 0.5, DV –3.0 and –2.2; AP +0.5, ML ±0.5, DV –2.8 and –2.0; AP –0.2, ML ±0.5, DV –2.5 and –2.0 from bregma, 0.5 μl per site), or mPFC (AP +3.8, ML ±0.5, DV –1.5; AP +3.3, ML ±0.5, DV –3.0 and –1.5; AP +2.6, ML ±0.5, DV –1.5; anteroposterior and mediolateral coordinates from bregma, dorsoventral coordinate from dura, 0.5 μl per site), incisor bar at –3.3 mm (*37*), using 0.09 M quinolinic acid, which produces AcbC lesions that spare Acb shell neurons (*25*). Sham lesions were made in the same manner, except that vehicle was infused.
22. Rats were retested on the basic task for seven sessions to obtain a baseline of performance. Next, all delays were removed to establish whether the rats remained sensitive to the delays. Four sessions were given in which all delays were omitted in alternate sessions (counterbalanced across groups). Further behavioral tests included (i) repetition of the delay-omission test (three sessions with delays present and three sessions with no delays, counterbalanced); (ii) six further sessions with no delays, to establish rats' preference between the two reinforcers in a simple choice situation; and (iii) reintroduction of delays for a further six sessions. In the mPFC and AcbC experiments, locomotor activity was measured in wire cages equipped with infrared beams enabling movements to be registered. Rats were placed in these unfamiliar cages and activity was recorded for 2 hours. Finally, food consumption was measured in the home cage over 4 days. Rats were allowed free access to either 45-mg sucrose pellets or their maintenance chow for 30 min. The time taken to consume either 50 sucrose pellets or an equivalent mass of chow was recorded.
23. The statistical techniques used have been described elsewhere (*13*). Graphs show group means; error bars are ±1 SEM unless stated. Data were analyzed using analysis of variance (ANOVA); tests of significance were performed at $\alpha = 0.05$. For repeated-measures analyses, Mauchly's test of sphericity was applied and the degrees of freedom corrected using the Huynh-Feldt epsilon as appropriate. Where significant heterogeneity of variance was found, Mann-Whitney U tests were used instead of ANOVA for simple effects comparisons, whereas the Box correction was applied for between-group comparisons.
24. Rats were overdosed with pentobarbitone and perfused transcardially with phosphate-buffered saline and 4% paraformaldehyde. Their brains were removed, postfixed, cryoprotected in 20% sucrose, cut at 60 μm, stained with cresyl violet, and assessed. Nine rats were excluded as their lesions were inaccurate. Final group sizes were 9 (ACC), 12 (ACC sham), 11 (mPFC), 10 (mPFC sham), 10 (AcbC), and 10 (AcbC sham). For lesion schematics, see *Science* Online (www.sciencemag.org/cgi/content/full/1060818/DC1).
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Conditional Restoration of Hippocampal Synaptic Potentiation in GluR-A–Deficient Mice

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Plasticity of mature hippocampal CA1 synapses is dependent on L-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors containing the glutamate receptor A (GluR-A) subunit. In GluR-A–deficient mice, plasticity could be restored by controlled expression of green fluorescent protein (GFP)–tagged GluR-A, which contributes to channel formation and displayed the developmental redistribution of AMPA receptors in CA1 pyramidal neurons. Long-term potentiation (LTP) induced by pairing or tetanic stimulation was rescued in adult GluR-A$^{-/-}$ mice when ^{GFP}GluR-A expression was constitutive or induced in already fully developed pyramidal cells. This shows that GluR-A–independent forms of synaptic plasticity can mediate the establishment of mature hippocampal circuits that are prebuilt to express GluR-A–dependent LTP.

Of the four AMPA receptor subunits (GluR-A to GluR-D) constituting one family of glutamate-gated ion channels (*1–3*), GluR-A is essential for adult hippocampal LTP but not for spatial learning in a water maze task (*4*). Studies on mice lacking GluR-A provided evidence that after tetanic stimulation, increased transmission at Schaffer collateral (SC/CA1) synapses is established by an augmented response of AMPA receptors. The selective, strong reduction of somatic AMPA receptor currents in GluR-A–deficient mice