Waiting for better things

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We and other animals act in order to obtain rewards, be they primary biological rewards such as food, shelter, and sex, or more complex social or personal goals. When animals act, they are sometimes rewarded (or reinforced) immediately, but often this is not the case. A foraging animal must choose an area in which to search for food, and a predator must choose which prey to stalk; in both cases, the final moment of acquiring food may be some time off when the decision is made. Humans regularly make financial and career decisions based on outcomes that are years or even decades away. To be successful, then, 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. Offered the choice between two identical rewards, one available now and one available some time off, animals consistently and sensibly prefer the immediate reward. However, if the delayed reward is bigger than the reward available immediately, it may be preferable to wait and obtain the larger payoff.

Furthermore, 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 (Ainslie, 1975). Impulsivity has long been recognized as a normal human characteristic (Aristotle, 350 BC / 1925) and in some circumstances it may be

beneficial — for example, someone with impulsive personality traits may be well placed to take advantage of unexpected opportunities (Evenden, 1999b). However, impulsive choice contributes to deleterious states such as drug addiction (e.g. Poulos *et al.*, 1995; Bickel *et al.*, 1999), in which drug addicts may forego long-term good health for the immediate reward of their drug. Children with attention-deficit / hyperactivity disorder (ADHD) also exhibit impulsive choice (see Sagvolden & Sergeant, 1998). In this article I will discuss briefly the neurobiological systems that play a part in determining the effects of delayed reinforcement, and which may therefore contribute to pathological impulsivity.

Neurochemistry of delayed reinforcement

One major avenue of research into impulsivity has concerned the brain's neuromodulator systems. These systems do not convey vast amounts of highly specific information (in the way that, say, the optic nerve conveys visual information); instead, they comprise small groups of neurons that project to wide areas of the brain, releasing chemicals that influence the behaviour of these other brain regions. Two such systems are the serotonin (5HT) and dopamine neurotransmitter systems; both of these have been implicated in the ability to choose delayed rewards.

The suggestion that 5HT is involved in impulse control followed originally from the observations that drugs that suppress 5HT function appeared to reduce animals' ability to inhibit inappropriate behaviour (motor acts). Animals with suppressed 5HT function continued to respond even if their responding was punished, or if they had to withhold a response to obtain reward. Thus, suppressing 5HT made animals disinhibited, or more impulsive in a 'motor' sense (see Thornton & Goudie, 1978; Soubrié, 1986; Evenden, 1999b; Evenden, 1999a). Additionally, low levels of the 5HT metabolite 5-hydroxyindoleacetic acid (5HIAA) in cerebrospinal fluid (CSF), indicating low turnover of brain 5HT (see Feldman *et al.*, 1997, p. 357), are associated with impulsive aggression and violence in humans (Linnoila *et al.*, 1983), including violent suicide (Åsberg *et al.*, 1976; Åsberg, 1997; Cremniter *et al.*, 1999). Low 5HIAA is also associated with risk-taking behaviour in monkeys — monkeys

with lower 5HIAA levels make longer and more risky leaps through the forest canopy (Mehlman *et al.*, 1994). In fact, depletion of 5HT from the forebrain causes animals to make impulsive choices in a variety of tasks (e.g. Wogar *et al.*, 1993). It is normal that delayed rewards are valued somewhat less than immediate rewards, all other things being equal (known as 'temporal discounting' of future rewards), but 5HT depletion has been suggested to steepen the temporal discounting function — meaning that delayed rewards lose their capacity to motivate or reinforce behaviour. The 5HT-depleted animal becomes hypersensitive to delays, or hyposensitive to delayed reward. As delayed rewards have unusually low value, the animal consistently chooses small, immediate rewards over large, delayed rewards, like an impulsive person. Conversely, increasing 5HT function with the 5HT indirect agonist fenfluramine has the opposite effect, decreasing impulsive choice (Poulos *et al.*, 1996). However, it should be noted that the effects of 5HT manipulations have not always followed this general pattern (see Cardinal *et al.*, 2004). For example, feeding humans a diet low in the amino acid tryptophan, which reduces central 5HT levels, may increase 'motor' impulsivity (Walderhaug *et al.*, 2002), but it has not been shown to increase impulsive choice in humans (Crean *et al.*, 2002); there is good evidence that not all types of impulsivity are promoted by low 5HT function in a simple way (Evenden, 1999b; Dalley *et al.*, 2002).

Of course, altered 5HT function has also been strongly implicated in depression (e.g. Delgado *et al.*, 1990; Feldman *et al.*, 1997, pp. 842-847; Caspi *et al.*, 2003), but the relationship between depression, impulsivity, and 5HT is complex. The precise neurochemical abnormality or set of abnormalities in depression is far from clear (e.g. Feldman *et al.*, 1997; Dhaenen, 2001; Stockmeier, 2003). There is no clear-cut relationship between depression itself and levels of 5HIAA in the CSF (Åsberg, 1997; Feldman *et al.*, 1997, p. 843), although antidepressant drugs themselves tend to lower CSF 5HIAA (see Bäckman *et al.*, 2000). However, there is a consistent association between low CSF 5HIAA and suicidal behaviour — not only in depression, but also in schizophrenia and other disorders (see Traskman-Bendz *et al.*, 1986; Cooper *et al.*, 1992; Åsberg, 1997; Cremniter *et al.*, 1999). Patients who are prone to suicide (many of whom are depressed) show high

impulsivity (Plutchik & Van Praag, 1989; Apter *et al.*, 1993; Corruble *et al.*, 2003). Thus, low 5HT function has been linked with impulsive behaviour, which is a risk factor for suicide, and abnormalities of the 5HT system are also associated with depression, also a strong risk factor for suicide.

The dopamine neuromodulator system also plays a role in animals' ability to choose delayed rewards; specifically, dopamine appears to promote the choice of delayed reinforcement via D2-type dopamine receptors (Wade *et al.*, 2000). This is in keeping with the observation that psychostimulant drugs such as amphetamine and methylphenidate (Ritalin®) can be an effective therapy for ADHD (Bradley, 1937). These drugs release monoamine neurotransmitters such as dopamine from neurons, and prevent their subsequent reuptake from the synapse back into the neuron. However, these are complex drugs and their mechanism of action is not wholly clear cut. For example, it appears that whether psychostimulants promote or reduce impulsive choice depends on the environmental conditions, such as whether the animal is given an explicit signal indicating the that the delayed reward is on the way or must simply wait for the delayed reward with no overt environmental cue (Cardinal *et al.*, 2000). Furthermore, some of actions of psychostimulants in this regard may be through their effects on 5HT as well as dopamine neurotransmission (Winstanley *et al.*, 2003).

Neuroanatomy of delayed reinforcement

Little is known anatomically about how the brain learns from or chooses delayed reinforcement. We studied three brain regions previously implicated in other kinds of reinforcement learning: the nucleus accumbens core (AcbC), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC) (Cardinal *et al.*, 2001). The AcbC is a critical site where signals that predict reward have their motivational impact (see Cardinal *et al.*, 2002). All three structures are abnormal in humans with ADHD or in animal models of ADHD (see Cardinal *et al.*, 2003), and all three receive projections from both the dopamine and serotonin neuromodulator systems (Fallon & Loughlin, 1995; Halliday *et al.*, 1995; Pickel & Chan,

1999). All, therefore, were candidate structures that might mediate choice involving delayed rewards.

To establish whether abnormalities in these regions might cause impulsive choice, we used a task in which hungry rats regularly choose between two levers. Responding on one lever led to the immediate delivery of a small food reward; responding on the other led to a much larger food reward, but this reward was delayed for between 0 and 60 seconds (Evenden & Ryan, 1996). Once they had been trained on this task, we selectively destroyed neurons of the AcbC, ACC, or mPFC, and re-tested the rats.

Rats with AcbC lesions became, and remained, impulsive; they began to choose the immediate, small reward much more often than sham-operated controls. They persisted in choosing impulsively, even though they were made to experience the larger, delayed alternative at regular intervals. Why did they do this? In theory, impulsive choice might arise for a variety of reasons. Take an abstaining smoker, offered a cigarette. His choice is between a small, immediate reward (a cigarette) and a large, delayed reward (better health in the future). If he acts impulsively where another does not, it could be because he does not perceive the larger reward to be as worthwhile as his self-controlled counterpart does, or because he is simply less influenced by outcomes that are delayed considerably. Which is true of rats whose AcbC has been destroyed? Our findings (Cardinal *et al.*, 2001; 2003) and others' (Balleine & Killcross, 1994; Brown & Bowman, 1995) suggest the latter. Even those AcbC-lesioned rats who showed an extreme preference for the larger reward when it was not delayed were incapable of choosing it as often as normal rats when it was delayed (Cardinal *et al.*, 2001; 2003). In fact, accumbens-lesioned rats appear just as sensitive to the magnitude of reward as normal rats (Brown & Bowman, 1995), suggesting that their impulsive choice arises not because the large reward is subjectively too small to compensate for the normal effects of the delay, but because they would have to wait too long for it.

In contrast, we found that damage to the ACC or mPFC did not produce impulsive choice. So although the ACC and mPFC have been shown to be abnormal in disorders of

impulsivity, our findings suggest that dysfunction of these regions is not an important contributor to impulsive choice. The abnormalities observed in these regions in the brains of people with ADHD may therefore be responsible for other features of the disorder (such as inattention or an inability to suppress motor acts), or these regions may have altered as a consequence of a disease process beginning elsewhere. Recent evidence has indicated that rats' propensity to choose delayed rewards is, however, altered by damage to the basolateral amygdala or orbitofrontal cortex (Mobini *et al.*, 2002; Winstanley *et al.*, 2004), two other structures that send information to the AcbC. A clearer understanding of the neurochemical and neuroanatomical abnormalities that underlie the symptoms and signs of clinical disorders of impulsivity may lead to more effective therapy.

While our study (Cardinal *et al.*, 2001) examined the role of the AcbC in choosing delayed rewards, it did not address whether the AcbC is also a critical structure for *learning* from delayed reinforcement. It is one thing to choose between rewards that differ in the amount of time you must wait to obtain them — like a hungry connoisseur who is also an expert chef choosing between cooking beef bourguignon and eating in 2 hours (a delayed but considerable reward), or cooking a frozen pizza and eating in 15 minutes (an early but lesser reward). Though the rewards differ in their delay, the cook is certain to achieve either goal and is in no doubt as to the relationship between his actions and the final result; he must merely choose which he prefers. It is another thing to work out which of your actions are the ones actually leading to particular outcomes. Consider someone manoeuvring a Venetian gondola for the first time — a long, heavy hand-powered vessel, powered and steered by a single small oar, pressed against (but not attached to) a complicated rowlock at one side of the boat. The novice gondolier must determine which oar motion to use in a given situation, yet the gondola's inertia means that it takes several seconds for each action to have a perceptible effect. The hapless novice must wait to see if his action was the correct one and, of course, must learn the task while being free to change tactics at any time.

How do animals accomplish this difficult task of learning to act with delayed outcomes, and does the AcbC contribute to this process too? In order to learn which actions are the correct ones that eventually lead to reward, and which are not, some mechanism must 'bridge' the delay between action and outcome. We recently took two groups of hungry rats, one with AcbC lesions and one without, and presented them with two levers; one did nothing, while every press on the other lever delivered a single food pellet. For some rats, this pellet was delivered immediately; for others, it was delayed. Normal rats took longer to learn to press the lever when the reinforcement was delayed, which is not surprising (Dickinson *et al.*, 1992), but they learned successfully with delayed reinforcement. Rats with AcbC lesions were perfectly able to learn this task when there was no delay, but were profoundly impaired when there was a delay between action and outcome (Cardinal & Cheung, unpublished data).

Taken together, these results suggest that the AcbC is a reinforcement learning structure specialized for the difficult task of learning with, and choosing, delayed reinforcement. Further understanding of the mechanism by which it does so, or fails to do so, might provide insight into the pathology of a number of neuropsychiatric disorders. Behavioural neuroscientific techniques may make it possible to distinguish the brain regions that underlie different types of impulsivity (Evenden, 1999b), and to segregate the neural abnormalities that contribute to complex disorders such as ADHD and drug addiction.

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