Chapter 5: General discussion

5.1 OVERVIEW

The experiments described in this thesis addressed the role played by the AcbC in rats' ability to learn from delayed rewards, to perform previously learned actions for delayed rewards, to assess reward magnitudes, and to choose uncertain rewards, together with the role of the hippocampus in the ability to learn from delayed rewards and to choose delayed rewards. In this concluding chapter, the findings from these experiments will first be summarized briefly. The results have already been discussed in Chapters 2–4; in this chapter, their implications will be considered in the wider context of impulse control disorders and the neural mechanisms that underlie reinforcement.

5.2 SUMMARY OF RESULTS

5.2.1 Role of the AcbC in learning with delayed reward

In Chapter 2 (Cardinal & Cheung, 2005), it was shown that excitotoxic lesions of the AcbC did not prevent rats from learning a simple instrumental response when the reinforcing outcome followed their action immediately. However, AcbC lesions impaired rats' ability to learn the same instrumental response when the outcome was delayed by 10 or 20 s. Increasing delays impaired learning in normal rats to some degree, which is a well-known finding (Grice, 1948; Lattal & Gleeson, 1990; Dickinson *et al.*, 1992). 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. AcbC lesions also impaired performance of an instrumental response that was learned preoperatively, but again only when response–reinforcer delays were present.

The fact that pre-exposure to the context improves instrumental learning in normal rats (Dickinson *et al.*, 1992) suggests one possible mechanism by which AcbC lesions might retard learning when delays are present. When a reinforcer arrives, it may be associated either with a preceding response, or with the context. Therefore, in normal animals, pre-exposure to the context may retard the formation of context–reinforcer associations by latent inhibition, or it might serve to retard the formation of associations between irrelevant behaviours and reinforcement. Non-reinforced exposure to the context forces the subjects to experience a zero-response, zero-reinforcer situation, i.e. $P(outcome \mid no\ action) = 0$. When they are then exposed to the instrumental contingency, such that $P(outcome \mid action) > 0$, this prior experience may enhance their ability to detect the instrumental contingency $\Delta P = P(outcome \mid action) - P(outcome \mid no\ action)$. In one aversive Pavlovian conditioning procedure in which a CS was paired with electric shock, AcbC lesions have been shown to impair conditioning to discrete CSs, but simultaneously to enhance conditioning to contextual or background CSs (Parkinson *et al.*, 1999b), though not all behavioural paradigms show this effect (Levita *et al.*, 2002; Jongen-Relo *et al.*, 2003). It is therefore possible that enhanced formation of context–reinforcer associations may explain the retardation of response–reinforcer learning in AcbC-lesioned rats in the presence of delays.

Acb lesions have also produced delay-dependent impairments in a delayed-matching-to-position task (Dunnett, 1990; Reading & Dunnett, 1991). Their effects on the delayed-matching-to-sample paradigm

have also been studied, but a more profound and delay-independent deficit was observed, likely due to differences in the specific task used (Burk & Mair, 2001).

5.2.2 Role of the AcbC in assessing reward magnitude

Previous studies have found that excitotoxic lesions of the whole Acb do not prevent rats from detecting changes in reward value (Balleine & Killcross, 1994). Such lesions also do not impair rats' ability to respond faster when environmental cues predict the availability of larger rewards (Brown & Bowman, 1995), and nor does inactivation of the Acb with local anaesthetic or blockade of AMPA glutamate receptors in the Acb (Giertler *et al.*, 2004). The effects of intra-Acb NMDA receptor antagonists have varied (Hauber *et al.*, 2000; Giertler *et al.*, 2003). AcbC-lesioned rats can still discriminate large from small rewards (Cardinal *et al.*, 2003b; 2004). Similarly, DA depletion of the Acb does not affect the ability to discriminate large from small reinforcers (Salamone *et al.*, 1994; Cousins *et al.*, 1996; Salamone *et al.*, 2001), and systemic DA antagonists do not affect the perceived quantity of food as assessed in a psychophysical procedure (Martin-Iverson *et al.*, 1987). These studies suggest that AcbC lesions do not prevent rats from discriminating *qualitatively* between large and small rewards, and that DA antagonism does not alter quantitative reward magnitude discrimination. For the purposes of analyses involving reward delay, it is important to know whether AcbC lesions alter the *quantitative* perception of reward magnitude—e.g. whether such lesions alter the magnitude sensitivity parameter Q in the model of Ho *et al.* (1999). In Chapter 2 (Cardinal & Cheung, 2005), it was observed that excitotoxic AcbC lesions did not impair, but rather improved, rats' ability to allocate their responses across two schedules in proportion to the experienced reinforcement rate, even when the two schedules were identical except in the magnitude of the reinforcements they provide, suggesting their sensitivity to reinforcer magnitude is quantitatively no worse than shams'.

5.2.3 Role of the hippocampus in learning with and choosing delayed reward

As discussed in Chapter 1, a role of the hippocampus in learning with delayed reinforcement might be suspected, because there is good evidence that the hippocampus contributes to the representation of context (Hirsh, 1974; Good & Honey, 1991; Selden *et al.*, 1991; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Honey & Good, 1993; Jarrard, 1993; Kim *et al.*, 1993; Phillips & LeDoux, 1994; Phillips & LeDoux, 1995; Chen *et al.*, 1996; Maren & Fanselow, 1997; Anagnostaras *et al.*, 1999; Holland & Bouton, 1999; Good, 2002; Rudy *et al.*, 2002; Ito *et al.*, 2005) and, as discussed earlier, contextual conditioning is important in learning with delays. Since context–outcome associations are thought to hinder instrumental learning with delayed reinforcement through contextual competition (Dickinson *et al.*, 1992; Dickinson & Balleine, 1994), it follows that if H lesions impair the formation of associations involving the context, such lesions might reduce contextual competition and hence facilitate instrumental conditioning when there is an action–outcome delay.

Indeed, excitotoxic lesions of the H ameliorated the deleterious effects of response–reinforcer delays on instrumental learning (Chapter 3; Cheung & Cardinal, 2005). H-lesioned rats responded slightly less than controls in the absence of delays, but they became better at learning (relative to shams) as the delays increased, in a delay-dependent fashion. This may have been because the lesion hindered the formation of context–outcome associations, promoting response–outcome association instead.

Unexpectedly, in separate experiments H-lesioned rats exhibited impulsive choice, preferring an immediate, small reward to a delayed, larger reward (in a task based on that of Evenden & Ryan, 1996), even though they preferred the large reward when it was not delayed (Chapter 3; Cheung & Cardinal,

2005). Though a quantitative difference in sensitivity to reinforcer magnitude might explain these results, as discussed above (Ho *et al.*, 1999) (see Chapter 1, p. 40), H-lesioned rats were able to discriminate the large from the small reinforcer, and such evidence as exists suggests that H-lesioned rats perceive reward magnitude normally (Kesner & Williams, 1995; Gilbert & Kesner, 2002). These results may also be explained in terms of altered temporal perception (as discussed on p. 106), affecting choice prospectively or retrospectively. For example, a lesion that increased the speed of an "internal clock" (Gibbon *et al.*, 1997) might affect choice prospectively in this task (i.e. the lesioned subject perceives itself to be at a later time point in the session than it actually is; since the task used a delay for the LL reward that increased across the session, such an effect would hasten the within-session shift towards the SS alternative), or might affect retrospective choice (i.e. the lesioned subject experiences the delay to the large reinforcer as longer than it actually is, causing it to value the reinforcer less than shams). The evidence for the role of the hippocampus in temporal perception is inconclusive: some studies have found that aspirative hippocampal lesions did not affect timing behaviour (Rawlins *et al.*, 1983; Port *et al.*, 1986; Dietrich *et al.*, 1997; Dietrich & Allen, 1998), whereas others have suggested that lesions of the hippocampus or fimbria/fornix speed up an internal clock, or reduce the estimation of time periods when a stimulus being timed is interrupted (Meck *et al.*, 1984; Olton *et al.*, 1987; Meck, 1988; Hata & Okaichi, 1998; Wallenstein *et al.*, 1998). In any case, H-lesioned rats were better at learning with delayed reinforcement but worse at choosing it, suggesting that self-controlled choice and learning with delayed reinforcement tax different psychological processes.

5.2.4 Role of the AcbC in choosing uncertain reward

As discussed in Chapter 1, correlational studies have suggested that the Acb may also be involved in the processing of uncertain or probabilistic reinforcement (Fiorillo *et al.*, 2003; Aron *et al.*, 2004; Ernst *et al.*, 2004; Matthews *et al.*, 2004; Fiorillo *et al.*, 2005; Niv *et al.*, 2005; Tobler *et al.*, 2005), yet this issue had not previously been addressed in a controlled interventional study. In Chapter 4 (Cardinal & Howes, 2005), excitotoxic lesions of the AcbC were found to induce what might be characterized as risk-averse choice in rats. AcbC lesions did not prevent rats from discriminating a large reward from a small reward, or a certain reward from an uncertain reward. However, when offered the choice between a small/certain reward and a large/uncertain reward, AcbC-lesioned rats showed a reduced preference for the large/uncertain reward (compared to sham-operated controls) in their final pattern of postoperative choice. AcbC-lesioned rats exhibited a tendency to behave as if an uncertain outcome were less likely than was really the case. Together with studies examining the effects of AcbC lesions on delayed reinforcement, these results suggest that the AcbC contributes to reinforcement and choice particularly when the reinforcer is temporally distant or uncertain.

5.3 WIDER IMPLICATIONS

There is evidence that the AcbC is involved in the pathogenesis of impulsive choice: the integrity of the AcbC is critical for animals to tolerate delays to appetitive reinforcement (Cardinal *et al.*, 2001), to learn normally from delayed appetitive reinforcement (Cardinal & Cheung, 2005), and to choose uncertain appetitive reinforcement normally (Cardinal & Howes, 2005). Likewise, normal hippocampal function appears necessary for rats to choose delayed appetitive reinforcement normally (Cheung & Cardinal, 2005), although the hippocampus appears to make a different contribution to learning with delayed reinforcement. In addition to providing neuroanatomical insight into the normal process through which delayed and/or uncertain reinforcement affects behaviour, this finding suggests a mechanism by which dysfunc-

tion of these structures may contribute to addiction, ADHD, and other impulse control disorders. In this section, I will set the contribution of the hippocampus to delayed reinforcement in the wider context of theories of time-limited hippocampal memory storage, and discuss broader implications of the present findings regarding hippocampal and AcbC function for disorders of impulse control.

5.3.1 The hippocampus and time-limited memory storage

The involvement of the hippocampus in learning with delayed reinforcement was hypothesized (Chapter 1, p. 49; Chapter 3, p. 81) to be a consequence of its role in representing contexts. In turn, this may be due to the ability of the hippocampus rapidly to associate arbitrary stimuli (see Chapter 1, p. 34).

It is not known whether the delay-related contribution of the hippocampus to instrumental learning is permanent or transient. However, many types of memory that are initially dependent upon the hippocampus do not remain so. This concept originally stemmed from the observation of a temporally graded retrograde amnesia in humans following medial temporal lobe resection or more restricted hippocampal damage, with good memory for events long past but poor memory for relatively recent events preceding the insult, in addition to the more obvious profound anterograde amnesia (Scoville & Milner, 1957; Zola-Morgan *et al.*, 1986; Corkin *et al.*, 1997; Corkin, 2002). Similar effects were observed in many animal models involving lesions restricted to the hippocampal formation (see Squire *et al.*, 2001). These observations led to the hypothesis that the hippocampus is involved in consolidating memories held elsewhere (Scoville & Milner, 1957; Squire *et al.*, 1975; 1980; Squire, 1986; 1992; Squire *et al.*, 2001): recent memories are vulnerable to hippocampal damage, but with time they become independent of the hippocampus, perhaps depending instead on cortical sites.

The major competing view is the "multiple memory trace" hypothesis of Nadel & Moscovitch (1997). They argue that the duration of retrograde amnesia for human autobiographical episodes following medial temporal lobe damage is extremely long (25–40 years), implying that most humans throughout history would never have "fully" consolidated a memory, and that the retrograde amnesia may not even be temporally graded at all (i.e. that the hippocampus causes a "flat" retrograde amnesia, with loss of all memories that ever depended upon it). Nadel & Moscovitch (1997) consider the hippocampus to be permanently involved in the storage of autobiographical memories, taking the viewpoint that autobiographical memory, personal semantic memory, and "general" semantic memory (vocabulary, grammar, object recognition) are progressively less sensitive, in that order, to retrograde amnesia following medial temporal lobe lesions in humans. In their view, the hippocampus provides a permanent spatial or contextual "index" that helps to retrieve a given memory. One-off (e.g. recent) autobiographical memories are dependent upon their index for retrieval, so are vulnerable to hippocampal damage. Semantic information is extracted from repeated episodic experiences; therefore, semantic information—and well-rehearsed, i.e. old, autobiographical memory—is supported by multiple memory traces, and is less dependent upon the hippocampal "contextual index" for retrieval. Recent statements of this hypothesis have been provided by Nadel & Bohbot (2001) and Rosenbaum *et al.* (2001).

However, retrograde amnesia is difficult to study in humans, because it is necessarily done retrospectively—the experimenter must assess the subject's memory for recent and ancient experience after the onset of amnesia, but it is difficult to sample memory equivalently from different past time periods, and to know that these memories were of comparable "strength" before the event that caused amnesia. The ideal test to compare these two hypotheses therefore involves prospective studies in animals (see Murray & Bussey, 2001, for these and other important methodological issues). The majority of such studies have shown temporally graded retrograde amnesia following a variety of hippocampus, fornix, and entorhinal

cortex lesions (see Squire *et al.*, 2001), supporting the view that the hippocampus does play a transient role in the storage of at least some types of memory. Amongst these studies, electrolytic or excitotoxic lesions of the hippocampus produce a time-limited retrograde amnesia for contextually conditioned fear (see Anagnostaras *et al.*, 2001).

Thus, memories of certain kinds initially depend upon the hippocampus but with time they become independent of the hippocampus. Transient hippocampal involvement does not require memories to "move" in a physically arbitrary way; there are perfectly plausible ways in which a memory might depend on a structure only temporarily (e.g. McClelland *et al.*, 1995). Figure 52 illustrates one possible simple mechanism. Recent studies have provided direct support for the view that hippocampal–cortical interactions are involved in the consolidation of some types of memory (Maviel *et al.*, 2004).

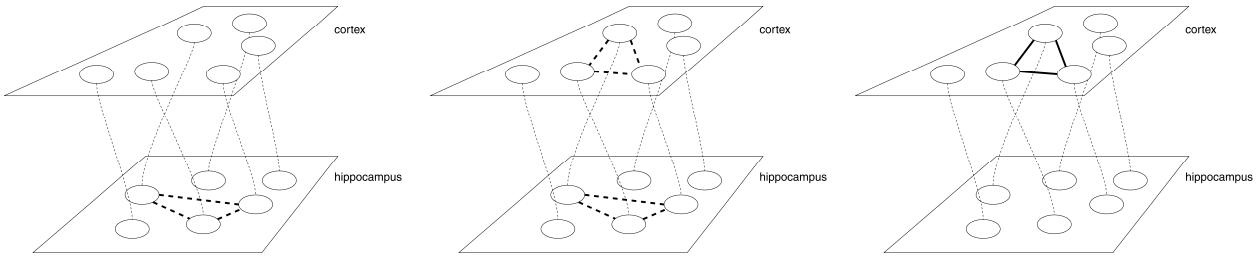

Figure 52: A simple mechanism for transient involvement of the hippocampus in memory storage

Left to right: schematics of how the hippocampus might interact with the cerebral cortex to consolidate memories "held" elsewhere. If the hippocampus exhibits rapid synaptic plasticity (but this is transient or easily disrupted) and the cortex exhibits slower but more stable plasticity, a plausible mechanism might proceed as follows. **Left:** hippocampal neurons have permanent connections to regions of neocortex (vertical dotted lines). A memory is formed by the hippocampus rapidly associating a number of active neurons, via synaptic plasticity (horizontal dashed lines). The memory is dependent upon the hippocampus. **Centre:** subsequent hippocampal activity promotes the firing of a cortical network that corresponds to the group of associated hippocampal neurons. As a direct result, this promotes an increase in the connectivity between the cortical neurons. **Right:** with time, the cortical links become strong enough not to require further hippocampus-driven consolidation. The memory is now independent of the hippocampus.

The impermanence of hippocampal memories has been demonstrated both at the behavioural and the synaptic level. Active processes appear to be involved in the decay of hippocampal memories. For example, Villarreal *et al.* (2002) have shown that systemic administration of the NMDA antagonist 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) blocks decay of hippocampal LTP; when given systemically between training and testing of performance in a radial 8-arm maze task known to depend on the hippocampus, CPP improved the retention of the memory, though it was not shown that this was due specifically to the drug's effect on the hippocampus. Perhaps decay of LTP, or long-term depression (LTD), which also depends on NMDA receptors (Dudek & Bear, 1992; Morris, 1994), is required to allow the hippocampus to acquire new memories, at the expense of old ones. If a rapidly associating network does not have the ability to lose old memories, there is catastrophic interference when new memories are laid down; this is the stability–plasticity dilemma familiar to connectionist modellers (Grossberg, 1982; McCloskey & Cohen, 1989). Rosenzweig *et al.* (2002) suggest that Villarreal *et al.* (2002) blocked exactly this loss of old memories with CPP.

Moreover, old memories that were once dependent upon the hippocampus can become so again. A "standard" view of consolidation would be that memories are created in a labile state (sometimes thought of as short-term memory, although this term has other uses), and with time, they are consolidated into a stable state (sometimes termed long-term memory). For example, electroconvulsive shock (ECS) or electroconvulsive therapy (ECT), which disrupts all ongoing electrical activity in the regions of the brain to

which current is applied, induces amnesia if given shortly after training, but not if given a long time after training (Duncan, 1949; Squire *et al.*, 1975). While the formation of new memories does not require protein synthesis, the consolidation of memories does; thus, administering the protein synthesis inhibitor anisomycin during contextual fear conditioning does not impair the memory of mice if they are tested one hour later, but that memory fades by 24 h as compared to a control group (see e.g. Abel *et al.*, 1997; Kandel, 2001). The same is true of hippocampal LTP: "early" LTP is not dependent upon protein synthesis, but it fades; normally, it is made long lasting by a second phase, "late" LTP, which requires protein synthesis (see Beggs *et al.*, 1999).

This view is extended by the concept of reconsolidation. As before, this hypothesis suggests that memories are created in a labile state and are consolidated into a stable state. However, in this theory, recalling or reactivating a memory *returns it to the labile state*. Therefore, although protein synthesis inhibitors or other amnestic treatments do not disrupt stable memories, they should be able to disrupt old memories that have been reactivated. Indeed, this has been observed (Misanin *et al.*, 1968). Recently, Nader *et al.* (2000) found that infusions of anisomycin into the BLA, a critical site of plasticity for CS–US associations involved in conditioned freezing in the rat, disrupted memory for a CS–US association that had been "retrieved" by presenting the CS. This disruption did not occur if anisomycin was given without representation of the CS. The molecular mechanisms of consolidation and reconsolidation are doubly dissociable (Lee *et al.*, 2004), so they are not exactly the same process. Reconsolidation is receiving considerable attention at the moment (Nader, 2003), partly because of the obvious clinical potential for selective memory "erasure"; if this were achieved safely it would have enormous implications for disorders in which aberrant memories play a prominent role, including obsessive–compulsive disorder (OCD), drug addiction, post-traumatic stress disorder, and so on. To date, few clinical studies have been based on the principle of reconsolidation. One notable exception is a series by Rubin *et al.* (1969; Rubin, 1976), who gave ECT to patients with OCD after reactivating their problematic compulsion, with apparently considerable success relative to conventional, non-reactivation ECT under anaesthetic. Some cautions have been raised, not all of them critical for the clinical implications; for example, some of the effects attributed to inhibition of protein synthesis have on occasion turned out to be due to unrelated side effects of particular drugs, with these side effects affecting consolidation or retrieval (Flexner *et al.*, 1963; 1967; Davis & Squire, 1984). Likewise, it has been a matter of enduring debate whether amnesia is a result of a storage deficit or a retrieval deficit (e.g. Warrington & Weiskrantz, 1970; Squire, 1980; Squire *et al.*, 1987). Many forms of amnesia can be reversed by reminder treatments, indicating that the memories were present all along and the deficit was one of retrieval (Millin *et al.*, 2001). Typical animal studies used ECS to induce amnesia; subsequent exposure to the CS, the US, or the ECS have all been shown to reverse the amnesia (Miller & Springer, 1972; Springer & Miller, 1972; Miller *et al.*, 1974; see Millin *et al.*, 2001). This applies equally to reconsolidation studies (Millin *et al.*, 2001): again, "reminder" effects occur, implying a retrieval deficit (Judge & Quartermain, 1982; Mactutus *et al.*, 1982; Debiec *et al.*, 2002).

This reconsolidation phenomenon has been termed "cellular reconsolidation", in which reactivation of a memory returns it to a labile state at the same neural site. A further phenomenon is "systems reconsolidation" (Debiec *et al.*, 2002), in which reactivation of a memory appears to make the memory depend upon a structure that it once depended upon before. Debiec *et al.* gave rats CS(context)–US(shock) pairings. Such associations are known to depend on the hippocampus early after learning, but with consolidation they become independent of the hippocampus (see above). After 45 days, they then presented the CS on its own (or not) and lesioned the hippocampus (or not). In the absence of CS presentation, the memory did not depend on the hippocampus (no effect of the lesion); presentation of the CS caused the memory to

depend on the hippocampus again, but only for ~48 hours. Debiec *et al.* suggest, based on these and other experiments, that a memory is formed, initially depends on the hippocampus, and during this time it can undergo "cellular" reconsolidation if activated. With time, the memory is consolidated in neocortex and no longer requires the hippocampus, unless it is reactivated, in which case it depends on the hippocampus for a while (albeit for a shorter time than during initial consolidation), and so on.

These time-limited memory storage phenomena are indirectly relevant to the issues of instrumental free-operant learning with delayed reinforcement and impulsive choice, though not specifically to their relationship with contextual conditioning (discussed in Chapter 3, p. 100). It is not known how the hippocampus contributes to performance of instrumental responses learned with delayed reinforcement. Hippocampal lesions made before training delay-dependently improved free-operant instrumental learning with delayed reinforcement (Figure 40, p. 92; Figure 42, p. 95) in that delays retarded learning less in H-lesioned subjects than in shams. If this was due to a hippocampus-dependent contextual memory competing with the instrumental response for association with the reinforcer, then since one would expect long-established contextual memories to have become relatively independent of the hippocampus (Anagnostaras *et al.*, 2001), it may be that pre-exposure to the experimental context, in addition to improving learning itself (Dickinson *et al.*, 1992), would reduce the effect of hippocampal lesions made before the instrumental learning task. Potentially, by the systems reconsolidation argument, contextual retrieval might increase the effects of hippocampal lesions again. It is more difficult to predict what would happen if hippocampal lesions were made after training on this task. If a contextual representation competes during *performance*, as well as learning, of an instrumental response, and the hippocampal lesion were made whilst that contextual memory was still dependent upon the hippocampus, then one would expect hippocampal lesions to produce a delay-dependent improvement in performance of a previously learned instrumental response, in addition to any delay-independent effects. The hippocampus appears to play a time-limited role in trace eyeblink conditioning (Takehara *et al.*, 2002); however, as discussed on pp. 100 and 103, the effects of hippocampal lesions on trace conditioning and instrumental conditioning with delayed reinforcement differ even when the lesions are made before training, and the conceptual relationship between the two tasks is not perfectly clear.

In the case of the impulsive choice task (Figure 43, p. 97), hippocampal lesions were made after 19 sessions of training on the task, when performance was stable and subjects were well trained. Since H lesions impaired subjects' ability to choose the large delayed reinforcer, this suggests (but does not demonstrate conclusively) that the hippocampus makes an enduring contribution to promoting the choice of delayed reinforcers. Finally, it is not known what the effects of hippocampal lesions made prior to training on this task would be. One would expect three competing effects: a relative delay-dependent enhancement of learning the action–outcome contingency for delayed reinforcement, a retardation of learning of this contingency at zero delay, and a reduction in preference for the delayed reinforcer.

5.3.2 ADHD

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 (Evenden, 1999b), and to segregate the neural abnormalities that contribute to complex disorders such as ADHD and drug addiction, as well as to normal variation in impulsive behaviour such as during adolescence (discussed later).

The integrity of the Acb is critical for animals to tolerate delays to appetitive reinforcement (Cardinal

et al., 2001; Cardinal & Cheung, 2005). In addition to being impulsive, AcbC-lesioned rats are also hyperactive (Maldonado-Irizarry & Kelley, 1995; Parkinson *et al.*, 1999a; Cardinal *et al.*, 2001; Cardinal & Cheung, 2005), but they do not appear to be inattentive: accuracy in tests of visuospatial attentional function is unaffected by AcbC lesions (Cole & Robbins, 1989; Christakou *et al.*, 2004). Destruction of the AcbC does not, therefore, mimic all the signs of ADHD, but these findings suggest that the behaviour of rats with AcbC damage resembles that of humans with the hyperactive–impulsive subtype of ADHD (APA, 2000).

The present results also suggest a role for the hippocampus in self-controlled choice (Cheung & Cardinal, 2005). Although the hippocampus has long been known to have a mnemonic role, the idea that the hippocampus plays a direct role in the selection of delayed rewards over immediate rewards appears novel, especially since the hippocampus does not appear to contribute to the association of actions with their outcomes over a delay. If anything, it appears to hinder this process (Cheung & Cardinal, 2005). Structural magnetic resonance imaging (MRI) studies have not shown differences in hippocampal volume between patients with ADHD and controls (Castellanos *et al.*, 1996; Filipek *et al.*, 1997), but adolescent girls with ADHD appear to have altered hippocampal glucose metabolism (Ernst *et al.*, 1997). Alterations in hippocampal function have been observed in a number of animal models of ADHD, including the coloboma mutant mouse and the neonatal rat hypoxia model (see Davids *et al.*, 2003); focal X-irradiation of the hippocampus in rats produces hippocampal granule cell ("microneuronal") hypoplasia and a syndrome of hyperactivity that also resembles ADHD (Diaz-Granados *et al.*, 1994). Ernst *et al.* (2003) found that adults with ADHD show less of a hippocampal blood flow increase than controls in a gambling game in which subjects were required to choose cards from decks that differed in the amounts and probabilities of gains and losses, akin to the Iowa gambling task of Bechara *et al.* (1994); however, choices involving reward delays were not examined.

In contrast, damage to other regions does not produce impulsive choice: for example, although the ACC, mPFC, and AcbSh have been shown to be abnormal in disorders of impulsivity (Papa *et al.*, 1996; Carey *et al.*, 1998; Ernst *et al.*, 1998; Papa *et al.*, 1998; Bush *et al.*, 1999; Rubia *et al.*, 1999; Sadile, 2000), damage to these regions does not produce impulsive choice in rats (Cardinal *et al.*, 2001; Pothuizen *et al.*, 2005). 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) (Muir *et al.*, 1996), 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.

5.3.3 Adolescent impulsivity

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 and mortality due to maladaptive behaviour (USA, 2001). Although adolescents are physically stronger and more resilient than children, morbidity and mortality increase 200% during adolescence, with the majority of the serious health problems related to difficulties with the control of behaviour and emotions; these problems include, for example, suicide, homicide, depression, and abuse of alcohol, nicotine, and other drugs (Dahl, 2004; Kelley *et al.*, 2004). In particular, adolescents may make choices that are rewarding in the very short term but poor in the longer term, i.e. impulsive. The adolescent Acb differs both in dopamine function and synaptic plasticity from that of the adult (see e.g. Andersen & Teicher, 2000; Philpot *et al.*, 2001; Schramm *et al.*, 2002). The hippocampus appears to

be more sensitive to ethanol, and may be more vulnerable to ethanol neurotoxicity, during adolescence (White & Swartzwelder, 2004). Similarly, development of the PFC (Giedd, 2004), inhibitory circuits in the PFC (Lewis *et al.*, 2004), and the projection from the amygdala to the PFC (Cunningham *et al.*, 2002) proceeds through this time, with PFC responsiveness also changing (Leslie *et al.*, 2004). If and how any such changes contribute to impulsive behaviour in adolescence (Adriani & Laviola, 2003) is at present unknown, though there are also demonstrable functional improvements during this time, such as in the ability to inhibit prepotent responses (see Luna & Sweeney, 2004).

5.3.4 Integration of AcbC functions with respect to impulsivity

Impulsivity is multifaceted, reflecting individual differences in distinct processes involving information gathering, the selection of outcomes, and the inhibition of motor actions (Evenden, 1999b). Furthermore, delay discounting and probability discounting may also reflect separate processes that both contribute to the selection of outcomes (see Chapter 1, p. 9). As discussed above, AcbC damage can produce impulsive choice, an impaired ability to choose delayed rewards (Cardinal *et al.*, 2001). In the context of choice involving uncertain appetitive reinforcement, "impulsivity" would equate to risk taking (less steep uncertainty discounting or greater willingness to choose unlikely rewards). AcbC lesions, however, have produced a risk-averse or conservative pattern of choice (Cardinal & Howes, 2005). Therefore, AcbC-lesioned rats cannot be characterized as impulsive in all senses. Instead, it seems that the AcbC promotes the selection, and perhaps the salience, of uncertain and delayed rewards—perhaps, in general, of rewards that are not certain, imminent, or present (Cardinal *et al.*, 2002a). The AcbC promotes choice of, and learning with, delayed rewards (Cardinal *et al.*, 2001; Cardinal & Cheung, 2005). It appears to promote the selection of uncertain reinforcers (Cardinal & Howes, 2005), and humans show increased Acb activation during the selection of high-risk options (Ernst *et al.*, 2004; Matthews *et al.*, 2004). The Acb is required for PIT, or the enhancement of instrumental responding by Pavlovian CSs signalling reward (Hall *et al.*, 2001; de Borchgrave *et al.*, 2002), for autoshaping, or approach to appetitive Pavlovian CSs (Parkinson *et al.*, 1999a; 1999b; 2000c; Cardinal *et al.*, 2002b; Parkinson *et al.*, 2002), for normal conditioned reinforcement, or working for CSs previously paired with reinforcement (Taylor & Robbins, 1984; 1986; Cador *et al.*, 1991; Parkinson *et al.*, 1999a), and Acb DA is required for the motivation to work hard (Ikemoto & Panksepp, 1999; Salamone & Correa, 2002; Salamone *et al.*, 2003; Mingote *et al.*, 2005; Salamone *et al.*, 2005).

What would one expect in an aversive context? As discussed earlier, increased probability discounting—a tendency to behave as if an uncertain outcome were less likely than it really is—would be expected to produce risk aversion for appetitive outcomes but risk proneness for aversive outcomes (Ho *et al.*, 1999). Similarly, enhanced delay discounting or temporal myopia would produce impulsive choice in an aversive context, impairing the ability to choose a small immediate penalty in preference to a large delayed penalty. In humans, at least, the delay and probability discounting processes appear similar for rewards and losses (Ostaszewski & Karzel, 2002; Green & Myerson, 2004). At present, it is not known whether AcbC lesions also affect choice involving delayed or uncertain outcomes in an aversive context; however, it is clear that the Acb is involved in aversive motivation (Salamone, 1994; Parkinson *et al.*, 1999b), including in the regulation of attention to stimuli predictive of aversive outcomes (Iordanova *et al.*, 2006).

5.3.5 Addiction

To consider the contribution of the AcbC and hippocampus to addiction, and the contribution of impulsive choice to addiction, I will first review major current theories of addiction.

5.3.5.1 Theories of addiction

In the context of the multifactorial psychological reinforcement learning framework described earlier (p. 2), the major neuropsychological theories of drug addiction—none of them mutually exclusive—can be summarized (Robbins *et al.*, 2005):

Direct positive effects of drugs; self-medication; tolerance

- Drugs are taken for their positive effects (positive reinforcement); that is, they have high instrumental incentive value. These positive effects may include euphoria, enhanced social experiences, enhanced intellectual or attentional performance, enhanced effects of other reinforcers (such as food or sex), and so on (see Wikler, 1965; 1973; Altman *et al.*, 1996; Feldman *et al.*, 1997). The precise effects depend on the drug class (Wise, 1996; Feldman *et al.*, 1997); for example, opiates such as heroin produce euphoria, and brain opioid systems may be directly involved in the assessment of "hedonic value" or pleasure (Berridge, 2000).
- An aspect of this may be that people "self-medicate" to achieve a desired level of mood, social performance, and so on (Khantzian, 1985; Weiss & Mirin, 1986; Altman *et al.*, 1996; Markou *et al.*, 1998; Newhouse *et al.*, 2004), although the extent to which self-medication of overt psychopathology occurs is debated (e.g. Castaneda *et al.*, 1994; Newhouse *et al.*, 2004). Furthermore, the effect of the drug depends upon the user's expectations (Mitchell *et al.*, 1996) and prior mood, and varies across people (Uhlenhuth *et al.*, 1981; de Wit *et al.*, 1986).
- Tolerance to pleasant drug effects may build up, requiring the user to take more drug to achieve the same effect. Tolerance can be due to a decrease in drug bioavailability ("metabolic tolerance"), a reduction in the number or responsiveness of receptors or intracellular mechanisms ("pharmacodynamic tolerance"), or a compensatory mechanism ("behavioural tolerance") (see Feldman *et al.*, 1997, p. 21). Tolerance may develop with chronic use, but in the case of cocaine, can develop in a single session (Fischman, 1989), perhaps explaining cocaine "bingeing". Metabolic tolerance is seen to barbiturates, ethanol and opiates (see Feldman *et al.*, 1997, p. 21). Pharmacodynamic tolerance is seen to a wide range of drugs including barbiturates, ethanol, opiates, amphetamine, cocaine, nicotine, and caffeine (see Feldman *et al.*, 1997, p. 21). Behavioural tolerance—conditioned tolerance—has been observed to opiates, ethanol, nicotine, benzodiazepines, and other drugs (Siegel, 1975; 1976; Krasnegor, 1978; Dafters & Anderson, 1982; Siegel, 1999). Since conditioned tolerance may be situation-specific, with the context serving as a CS, the lethality of drugs may be increased if the environment changes (Siegel, 1999).

Conditioning and sensitization

- CSs associated with the pleasant aspects of drug taking may act to promote drug taking. Drug-associated cues (including mood states, people, locations, and abuse paraphernalia) may induce some of the primary effects of drugs (Kenny *et al.*, 2003), but can also induce craving in addicts, and trigger relapse (Siegel, 1988; Tiffany & Drobes, 1990; Gawin, 1991; O'Brien *et al.*, 1998). Addicts may also work directly for drug-associated stimuli (conditioned reinforcement), leading them to the primary drug reinforcer.

- Sensitization ("inverse" or "reverse" tolerance) may also occur; this is where repeated doses of a drug enhance one or more of its effects. Prototypically, moderate, spaced doses of amphetamine enhance the subsequent locomotor response to amphetamine (Robinson & Berridge, 1993; Altman *et al.*, 1996; Kalivas *et al.*, 1998). Sensitization can exhibit environmentally specific (conditioned) properties (Post & Weiss, 1988), but sensitization regimes can also induce changes in drug pharmacodynamics (Pettit *et al.*, 1990). It has been suggested that the ability of drug-associated CSs to promote drug seeking or craving also sensitizes as a consequence of repeated drug taking (Robinson & Berridge, 1993; Wyvell & Berridge, 2001). Amphetamine sensitization also enhances the subsequent development of habits (Nelson & Killcross, 2006), discussed below.

Withdrawal and conditioned withdrawal

- Some drugs, notably the opiates and alcohol, produce powerful physical withdrawal syndromes, which are aversive. Withdrawal symptoms are improved by the drug, so the drug is taken to avoid or escape from withdrawal (negative reinforcement) (Wikler, 1965; 1973). Here, incentive learning operates for drugs of abuse just as for natural reinforcers. Just as hunger, a natural motivational state, increases the hedonic impact of foodstuffs (Berridge, 1991) and this in turn teaches the animal that it is worth working for those foodstuffs more when it is hungry (Dickinson & Balleine, 1994), opiate withdrawal reflects a "new" motivational state that the animal can perceive interoceptively, and rats have to learn that heroin has a high value in the state of opiate withdrawal (Hutcheson *et al.*, 2001a). The hedonic impact of a reinforcer may be a "common currency" for determining the value of widely different reinforcers (e.g. Cabanac, 1992).
- Environmental stimuli may become associated with withdrawal (Goldberg & Schuster, 1967; O'Brien *et al.*, 1975; 1976; 1977); CSs for withdrawal may then provoke drug taking just as withdrawal itself does (Wikler, 1965; 1973).
- Drugs such as cocaine that do not produce obvious physical withdrawal syndromes may nonetheless have unpleasant after-effects on mood (dysphoria) (Koob & Bloom, 1988; Gawin, 1991; Markou & Koob, 1991; Koob *et al.*, 1997; Knackstedt *et al.*, 2002), which may promote drug taking in the same way that physical withdrawal does. "Opponent process" theories (Solomon & Corbit, 1973; 1974; Solomon, 1980a; 1980b; Koob *et al.*, 2004) use the idea that a long-lasting anhedonic or dysphoric (i.e. unpleasant) process opposes the euphoric effects of drugs, and that with chronic use, the euphoric effects diminish and the dysphoric process comes to dominate, leading to drug taking via negative reinforcement.

Habit learning

- Drugs may activate habit-learning systems directly, so that actions that led to the drug are directly reinforced, creating powerful stimulus–response habits or "involuntary" responding, faster than with natural reinforcers (O'Brien & McLellan, 1996; Tiffany & Carter, 1998; Robbins & Everitt, 1999; Everitt *et al.*, 2001; Everitt & Wolf, 2002). A hallmark of habitual (as opposed to goal-directed) responding is that it persists even if the reinforcer's value is reduced (Dickinson, 1994). Habits are sometimes thought of as "compulsive" responding when they occur at an abnormally high level, since they do not depend on the current value of the goal. Alcohol seeking may reflect primarily habitual responding (Dickinson *et al.*, 2002), and while cocaine seeking can be goal directed (Olmstead *et al.*, 2001), under some circumstances responding for cocaine can be less susceptible to devaluation of the reinforcer (that is, more habitual) than responding for natural reinforcers (Miles *et al.*, 2003). Simi-

larly, soon after acquisition, cocaine seeking behaviour is readily suppressed by an aversive CS, whereas following prolonged experience of cocaine, this conditioned suppression is lost (Vanderschuren & Everitt, 2004). Psychostimulant sensitization also enhances subsequent habit formation (Nelson & Killcross, 2006). Craving and habits both capture something of the casual definition of addiction as "compulsive" behaviour (e.g. APA, 1994; Leshner, 1997; Koob *et al.*, 1998a).

Individual vulnerability

- People who become drug addicts may be more vulnerable than other people to one or more of these neuropsychological effects, as well as being more predisposed to try drugs of abuse in the first place.

Comparison of drug taking to alternative activities

- At a higher level of analysis, with a behavioural economic perspective, addicts weight up the benefits and costs of drug taking. They may do so rationally (Stigler & Becker, 1977; Becker & Murphy, 1988), or may exhibit decision-making flaws characteristic of humans, such as focusing inappropriately on short-term rather than long-term goals and being inconsistent in their choices (Ainslie, 1975; 1992; Herrnstein & Prelec, 1992; Heyman, 1996; Rachlin, 1997; 2000a; Ainslie, 2001).
- Drug addicts may be predisposed to act even more for short-term benefit than other people, or drugs may induce decision-making deficits in regular users (Petry *et al.*, 1998; Bickel *et al.*, 1999; Madden *et al.*, 1999; Rogers *et al.*, 1999a; Volkow *et al.*, 1999; Ainslie & Monterosso, 2003; Bickel & Johnson, 2003; Mitchell, 2003; Vuchinich & Heather, 2003); for example, as discussed earlier (p. 18), there is some evidence that self-control deficits may be a reversible consequence of cigarette dependence (Bickel & Johnson, 2003).

None of these theories, or indeed levels of explanation, is adequate on its own (Heather, 1998). For example, although heroin may be taken to alleviate withdrawal, heroin self-administration can persist in the absence of withdrawal (Bozarth & Wise, 1981; 1984), and although heroin has euphoric effects, humans will work for doses that they cannot subjectively distinguish from placebo (Lamb *et al.*, 1991). However, to focus on or seek a single theory of drug addiction is to miss the point that drugs of abuse have many effects, people take drugs for many reasons, and those reasons vary across people.

5.3.5.2 Behavioural economic approaches to addiction

To bridge the gap between neuroscientific and behavioural economic approaches to addiction, a little further elaboration of the behavioural economic approach is necessary. A direct application of traditional economics to addiction is the calculation of *elasticity of demand* for goods, such as drugs. A "good" is a commodity that, all other things being equal, agents prefer more of to less. In a barter economy, and therefore in animal experiments, the "price" of a commodity has no absolute meaning; we can speak of price only in terms of what other commodities an animal will give up to obtain the good, and that may depend on the specific commodities being traded (Friedman, 1990; Rachlin, 2003; Vuchinich & Heather, 2003). In humans, elasticity has an more general meaning, since humans use a monetary economy. Money is a single commodity that is substitutable for almost all others (is fungible), so we can calculate elasticity as the change in consumption as monetary price changes. *Own-price elasticity* measures the change in consumption of a good as its price changes. Formally,

$$\varepsilon = \frac{\%\text{ small change in quantity consumed}}{\%\text{ small change in price}} = \frac{\Delta q}{Q} \div \frac{\Delta p}{P} = \frac{\Delta q}{\Delta p} \cdot \frac{P}{Q} = \left(\frac{P}{Q}\right)\frac{\mathrm{d}Q}{\mathrm{d}P}$$

To take a simple example, suppose that biscuits cost £0.10 each, and I eat 100 biscuits/week; this costs me £10/week. If the price doubles to £0.20, I could do several things. I could halve my weekly consumption to 50 biscuits, so I continue to spend £10/week. This would be called *unit elasticity* ($\varepsilon = -1$). I could reduce my consumption by more than this, saving money. This would be *elastic* demand ($\varepsilon < -1$): my demand is very sensitive to price. Or I could not cut back very much, say to 90 biscuits/week, spending more money in total; this would be *inelastic* demand ($-1 < \varepsilon$). If demand were totally inelastic, I would consume the same no matter what the price ($\varepsilon = 0$). For most goods, demand is inelastic at low prices and elastic at high prices, termed "mixed" elasticity. *Cross-price elasticity* measures the consumption of a good as the price of other goods changes. Some commodities are *substitutes*, like butter and margarine. If the price of butter goes up, we may buy more margarine instead ($\varepsilon > 0$). Some commodities are *complements*, like gin and tonic. If the price of gin goes up, gin drinkers may buy less tonic, because they buy less gin ($\varepsilon < 0$). Some commodities are *independent*, like butter and computers, where the price of one doesn't affect consumption of the other ($\varepsilon = 0$).

An obvious way to think about addiction is that demand for drugs is inelastic compared to demand for other things. The more someone is addicted, the more inelastic their demand is; if the price increases, they will therefore sacrifice other commodities such as work, money, or social interaction, rather than sacrifice their drug. For example, alcohol demand in rats can be more inelastic than demand for food (Heyman *et al.*, 1999; Heyman, 2000). Yet drug demand is certainly not completely inelastic, and addiction is not an all-or-nothing phenomenon. Most users of heroin, cocaine, and alcohol do not use extremely large amounts, as the stereotype of an addict would suggest. Instead, most use infrequently, or "chip" (NHSDA, 2001; MacCoun, 2003b). Furthermore, most (>75%) of those dependent on an illicit drug recover (Warner *et al.*, 1995; Heyman, 2003). In fact, the elasticity of demand for cigarettes is typically about –0.4 (Gruber *et al.*, 2002; Chaloupka *et al.*, 2003); that is, if the price goes up by 10%, consumption goes down by 4%. This is for two reasons. First, when price goes up, some people quit altogether (termed *participation elasticity*). Second, people who continue to smoke, smoke less (termed *conditional elasticity of demand*, or elasticity given that someone uses the drug at all).

As for most commodities, the elasticity of drugs of abuse varies with price. Smokers working for cigarette puffs in the laboratory are fairly inelastic when the price is low ($\varepsilon = -0.56$ at a price ranging between 12–1600 responses per puff), but become more elastic when the price goes up ($\varepsilon = -1.58$ at a price ranging between 400–4500 responses per puff) (Bickel *et al.*, 1995b; DeGrandpre & Bickel, 1995; Chaloupka *et al.*, 2003). Probably for this reason, elasticity is greater for poorer smokers, for whom cigarettes are proportionally more expensive (Gruber *et al.*, 2002). In the UK, national elasticity of demand for alcohol ranges from about –1.69 for wine through –0.86 for spirits to –0.76 for beer (Smith, 1999). Participation price elasticities (the effect of price on the number of people using a drug) are about –0.90 to –0.80 for heroin and –0.55 to –0.36 for cocaine; overall elasticities (the effect of price on the total amount consumed) are about –1.80 to –1.60 for heroin and –1.10 to –0.72 for cocaine (Saffer & Chaloupka, 1995). Elasticity also varies with motivational state and other factors. Animals' demand for food is more inelastic when they are hungry and if there are no alternative ways of obtaining food (e.g. Hursh, 1978); similarly, demand for cigarettes is more inelastic when smokers have been abstinent (Madden & Bickel, 1999). When considering drug policy, it is also important to consider cross-price elasticity: if a policy reduces consumption of drug A, will the benefits be mitigated by increased consumption of drug B? In

the case of alcohol and cigarettes, the two are either complements ($\varepsilon < 0$) or independent, so reducing consumption of one tends to reduce (or not affect) consumption of the other (Gruber *et al.*, 2002). Similar analyses have been conducted for other drugs and non-drug reinforcers (Bickel *et al.*, 1995a).

Some leading economists have characterized addiction as being rational (Becker & Murphy, 1988), in that addicts take the future consequences of their behaviour into account and have stable preferences. In rational addiction theory, addiction arises because the quantities of the addictive good consumed at different time points are complements, which can lead to unstable states; this accounts, for example, for binges of consumption. Certainly, assuming rationality allows us to predict behaviour much better than not assuming rationality, unless we can predict the specific way in which people will be irrational (Friedman, 1990). A major contribution of rational addiction theory (Stigler & Becker, 1977; Becker & Murphy, 1988) was therefore to consider price as a major influence on the consumption of addictive drugs (MacCoun, 2003a). However, the premise that drug addicts choose rationally, maximizing their total happiness, has been criticized (e.g. Winston, 1980; Ainslie & Monterosso, 2003; MacCoun, 2003a). Certainly, humans do not always choose according to rational norms, as discussed in Chapter 1 (p. 1). Since hyperbolic temporal discounting is a feature of human and animal intertemporal choices (Chapter 1, p. 9), many major behavioural economic theories of addiction (Ainslie, 1975; 1992; Herrnstein & Prelec, 1992; Heyman, 1996; Rachlin, 1997; 2000a; Ainslie, 2001) emphasize that addiction results from the maximization of short-term rather than long-term utility (see MacCoun, 2003a; Vuchinich & Heather, 2003), with preferences that are inconsistent over time thanks to hyperbolic discounting, and that drug addictions

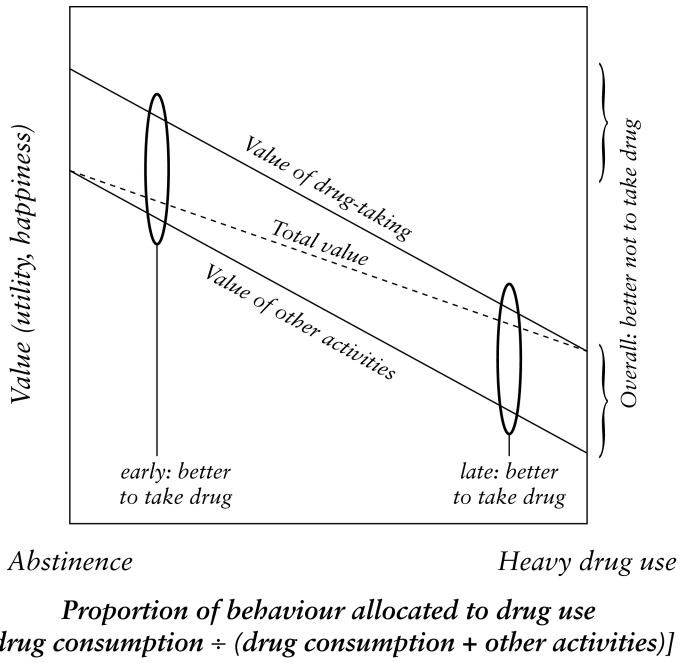

Figure 53: The "primrose path" to addiction

Good now, bad in the long run—the "primrose path" to addiction (Herrnstein & Prelec, 1992; Rachlin, 1997; 2003; Vuchinich & Heather, 2003). At any point, drug taking has a higher value than other activities, so you take the drug. But drug taking lowers both the value of future drug taking: for example, alcohol consumption causes tolerance, meaning that future alcohol isn't worth as much. Moreover, drug taking lowers the value of other activities: for example, the more alcohol you consume, the less you socialize and the worse you are at socializing; the more heroin you take, the worse you are at your job. So as you drink more, your total happiness goes down: you'd be better off not being an alcoholic. But even when you are an alcoholic, drinking now is worth more than not drinking now, for you are sensitive to local, not global, utility. As Rachlin (2000b) puts it: "The alcoholic does not choose to be an alcoholic. Instead he chooses to drink now, and now, and now, and now. The pattern of alcoholism emerges in his behaviour… without ever having been chosen."

(Rachlin, 2003) are bad ("negative" addictions) because short-term selection of drugs leads to lower long-term overall utility. Consumption of drugs reduces the value of future activities—the "primrose path" to addiction (Figure 53). Knowledge of one's own predisposition to be temporally inconsistent allows the use of self-control strategies (Ainslie, 2001; Ainslie & Monterosso, 2003; Homer, ~800 BC / 1996), such as precommitment to a particular course of action, which improve long-term utility.

Economic theories of addiction are also relevant when considering the extent to which drug use is voluntary. The diagnostic criteria for drug dependence (APA, 2000) include a compulsion to take the drug, yet drug use can certainly be voluntary. Drug use certainly has utility to the user; this may be in the form of euphoria, enhanced social experiences, or enhanced intellectual performance, depending on the drug (see Feldman *et al.*, 1997). It is debatable whether even addicts take drugs involuntarily: just because someone says they don't want to smoke and then later smokes doesn't mean they're smoking involuntarily—it might simply be that they're inconsistent (Schaler, 2000; Skog, 2003). Furthermore, not everyone who smokes wants to give up. Appreciating these differences leads to a broader classification of addiction than is conventional (Figure 54).

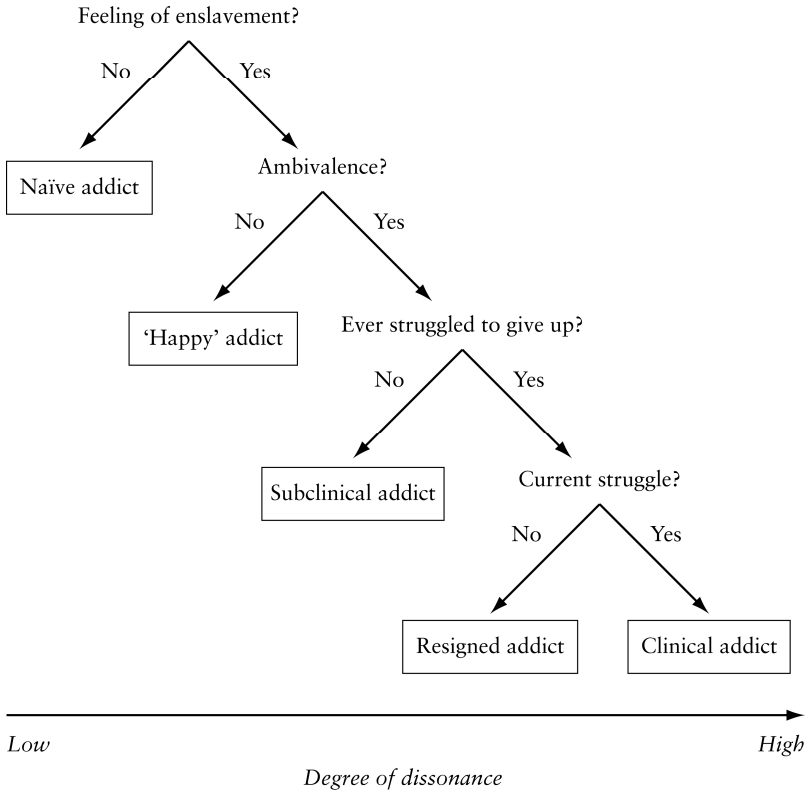

Figure 54: Skog's classification of addiction

Skog's (2003) view of addiction. A person may be unaware that it is difficult for him or her to live without a drug. Such a person is enslaved, but unaware; Skog calls them "naïve" addicts. He offers the example of a heavy drinker in Paris in World War II, who had never realised that he was dependent on alcohol until rationing came along and he was limited to one litre of wine per week. Then there are those who know that life would be harder without, but are happy with this situation: "happy" addicts, such as the 1950s smoker who thought that smoking was good for you (or at least, not bad). Those who are aware smoking is bad for you but feel no particular motivation to cut back are called "subclinical" addicts by Skog. Finally, there are those who have tried and failed but aren't trying at the moment, and those in an active struggle to quit.

The fact that people do not act to maximize their total, long-term expected reward can explain a number of otherwise counterintuitive results: for example, cigarette taxes can make smokers happier (Gruber &

Mullainathan, 2002). This implies that addiction is not "rational"—addicts' preferences are not consistent over time, and so cigarette taxes make smokers happier because they serve as a valuable self-control device, helping them to avoid smoking. Such self-control strategies are not merely a human phenomenon (Rachlin & Green, 1972; Ainslie, 1974; Ainslie & Herrnstein, 1981), as was discussed earlier. Drug addicts may discount the future more steeply (and therefore be even more impulsive and short-termist) than non-addicts (Petry *et al.*, 1998; Bickel *et al.*, 1999; Madden *et al.*, 1999; Ainslie & Monterosso, 2003; Bickel & Johnson, 2003; Mitchell, 2003; Vuchinich & Heather, 2003). Similar short-termism can explain relapse (Heyman, 2003): since one cigarette is unlikely to cause cancer and one shot of heroin doesn't condemn you to a junkie lifestyle, a person can correctly reason that since it's "just for one last time", the drug is the better choice. But a series of "one-last-times" turns into a relapse.

5.3.5.3 Contribution of the AcbC

In the context of addiction, impulsive choice plays a prominent role in maintaining the selection of drugs of abuse in favour of other, longer-term rewards (Poulos *et al.*, 1995; Heyman, 1996; Bickel *et al.*, 1999; Evenden, 1999a; Mitchell, 1999); see also p. 18. Drugs of abuse including opiates, ethanol, and psychostimulants can produce chronic adaptations in brain regions including the Acb (Koob *et al.*, 1998b), and chronic methamphetamine has been shown to increase impulsive choice in rats (Richards *et al.*, 1999a).

Furthermore, as discussed on p. 31, the motivational process provided by the AcbC (exemplified by PIT) has been suggested to be particularly significant in some addictions, perhaps becoming sensitized, and modification of this process may have therapeutic potential. If the suggestion that Pavlovian (cue-induced) motivational processes contribute to preference reversal effects and to addiction is correct (Loewenstein, 1996; Cardinal *et al.*, 2003b; Gjelsvik, 2003; Loewenstein & O'Donoghue, 2004), then the role of the AcbC is doubly important (see Cardinal *et al.*, 2002a). PIT requires the AcbC (Hall *et al.*, 2001), noncontingent CSs elevate AcbC DA levels (Bassareo & DiChiara, 1999; Ito *et al.*, 2000), DA antagonists block PIT (Dickinson *et al.*, 2000), and enhancement of Acb DA function boosts PIT (Wyvell & Berridge, 2000). PIT can also be amplified by CRH acting in the AcbSh (Pecina *et al.*, 2006), a potential mechanism through which stress may produce cue-triggered relapse in addiction. As noted above, the process of addiction is complicated further by the ability of drugs of abuse to alter the function of neural structures including the Acb (see Koob *et al.*, 1998b). Addictive drugs may be unique among reinforcers in producing sensitization, the phenomenon by which repeated drug administration leads to an enhanced response to the drug (Robinson & Berridge, 1993; Altman *et al.*, 1996; Kalivas *et al.*, 1998). Psychostimulant sensitization enhances the sensitivity of the Acb to DA stimulation (Cador *et al.*, 1995), and enhances PIT subsequently (Wyvell & Berridge, 2001).

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.

It is worth noting, however, that although a detailed knowledge of the operation of these neural systems may offer opportunities for pharmacological treatment of addiction (O'Brien, 1997), this might not change the fact that the simplest and most powerful way to influence these neural systems is often through conventional economic manipulations (MacCoun, 2003b). Nevertheless, one centre has attempted to treat addiction in humans by stereotaxic ablation of the Acb (Gao *et al.*, 2003). Citing experiments showing a reduction in heroin seeking and self-administration after AcbC lesions in rats (Alderson *et al.*, 2001; Hutcheson *et al.*, 2001b), Gao *et al.* made bilateral radiofrequency lesions of the Acb in 28 conscious recidivist opiate addicts. The authors comment that the subsequent relapse rate was markedly

lower than following the same subjects' previous detoxification attempts, after which 100% had relapsed within three weeks. Postoperatively, two subjects were lost to follow-up and were not analysed further; two (7.7% of those analysed) had relapsed within one month, 10 (38.5%) within six months, and 15 (57.7%) had relapsed by the time of publication, with those 11 (42.3%) subjects who were still abstinent beyond six months having been followed up for 8–15.5 months. Craving was apparently reduced, though no data were presented to support this assertion. This study is not a model of the scientific method: the trial was clearly neither blind nor randomized, and the control condition was the same subjects preoperatively. It is notable that the authors themselves reported improvements across their series of subjects, which they attributed to patient selection and preparation, lesion parameters, and post-discharge care; one alternative hypothesis, of course, would be that aspects of this process other than the lesion were responsible for some of the benefits. No subjects suffered intracranial bleeding or infection; side effects included "character change" (not otherwise specified) in two subjects and "slight symptoms" (not otherwise specified) in one of these, with non-disabling memory loss in four subjects. Neuropsychological data were not reported, and it is not clear whether a deficit in self control or in pursuing long-term goals was apparent.

One obvious question is raised by this set of studies. Destruction of the AcbC has been observed to reduce drug seeking in an animal model (Alderson *et al.*, 2001; Hutcheson *et al.*, 2001b); destruction of the Acb has been claimed to have similar effects in free-living humans (Gao *et al.*, 2003). Destruction of the AcbC produces impulsive choice in an animal model (Cardinal *et al.*, 2001). Impulsive choice is suggested to contribute to maladaptive behaviours including addiction (Poulos *et al.*, 1995; Heyman, 1996; Bickel *et al.*, 1999; Evenden, 1999a; Mitchell, 1999; Ainslie, 2001). Taken at face value, these three claims appear incongruent. There is insufficient evidence to resolve this question conclusively. However, the simplest explanation may be that AcbC lesions do more than produce impulsive choice. For example, such lesions impair free-operant responding for delayed rewards (Cardinal & Cheung, 2005), they impair PIT (Hall *et al.*, 2001; de Borchgrave *et al.*, 2002), and they affect conditioned reinforcement (Taylor & Robbins, 1984; 1986; Cador *et al.*, 1991; Parkinson *et al.*, 1999a), amongst other effects. In second-order schedules of reinforcement such as those used in the rat models of drug seeking cited (Alderson *et al.*, 2001; Hutcheson *et al.*, 2001b), responses are intermittently reinforced by a stimulus, and these stimuli are intermittently paired with primary reinforcement. Clearly, impairment of a cue-triggered motivational process or an inability to respond normally for conditioned reinforcers or delayed rewards might impair responding on such a schedule, independently of any effects on impulsive choice. In turn, choice impulsivity might be expected to play a more prominent role in a situation involving multiple reinforcers and genuine intertemporal choice. As was emphasized above, many factors contribute to addiction and to the selection of actions in general. It is likely that under different circumstances the AcbC both helps and hinders the pursuit of specific goals, such as a drug of abuse or any other reinforcer, as might be expected of a structure involved in making decisions about the best goal to pursue at a given moment.

5.3.5.4 Contribution of the hippocampus

Although hippocampal function is related in a number of ways to addiction, no studies to date have specifically related hippocampal dysfunction to addiction via a mechanism of impulsive choice. Likewise, while a number of studies have suggested an effect of chronic drug use on impulsivity (see p. 18), it is not clear that any such effect is mediated via the hippocampus.

The role of the hippocampus in addiction has most often been related to its role in contextual processing (see Robbins *et al.*, 2005). Theta-frequency (4–7 Hz) burst stimulation of the hippocampus (specifically, 100 Hz stimulation in five-pulse trains repeated at 5 Hz) has been shown to reinstate extinguished cocaine seeking in a manner that depended on glutamate transmission in the VTA. This has been sug-

gested to mimic the process by which reinstatement occurs when animals are placed in a context associated with drug taking, rather than in response to discrete cocaine cues (Vorel *et al.*, 2001). Dorsal hippocampal inactivation attenuates context-induced reinstatement of drug seeking, as does inactivation of the dorsal mPFC (Fuchs *et al.*, 2005). Hippocampal activity also correlates with the euphoriant effects of heroin (Sell *et al.*, 2000) and with craving for cocaine (Kilts *et al.*, 2001) or alcohol (Schneider *et al.*, 2001). Smoking-associated cues trigger hippocampal activation in nicotine-deprived smokers (Due *et al.*, 2002). Rats will self-stimulate the hippocampus electrically (Ursin *et al.*, 1966; Campbell *et al.*, 1978; Collier & Routtenberg, 1984; Campbell & Milgram, 1985) and will self-administer opioids into the hippocampus (Stevens *et al.*, 1991). Neonatal ventral hippocampal lesions have been shown to enhance simple instrumental conditioning for sucrose or cocaine subsequently in life (Chambers & Self, 2002), though the significance of this is unclear and the effects of neonatal ventral hippocampal lesions upon adult behaviour differ from the effects of lesions made in the adult (see Chambers & Self, 2002). Moreover, hippocampal, amygdala and PFC projections interact in the Acb in a way that is modulated by mesolimbic DA and that, in turn, can modulate the release of DA and influence input from other afferents to the Acb (O'Donnell & Grace, 1995; Blaha *et al.*, 1997; Floresco *et al.*, 1998; Floresco *et al.*, 2001a; Floresco *et al.*, 2001b). Thus, the hippocampus, amygdala, and PFC may influence drug seeking through their convergent projections to the Acb.

Hippocampal structure and function is altered by certain drugs of abuse, including cocaine (Thompson *et al.*, 2004; Yamaguchi *et al.*, 2004; Uz *et al.*, 2005; Yamaguchi *et al.*, 2005), nicotine (Abrous *et al.*, 2002), and opiates (Pu *et al.*, 2002). In particular, adult hippocampal neurogenesis is reduced by a number of drugs of abuse (reviewed recently by Eisch & Harburg, 2006). The relationship with addiction is unclear at present; however, parallels have been drawn with depression, in which hippocampal neurogenesis is also reduced (Kempermann & Kronenberg, 2003; Malberg & Duman, 2003; Duman, 2004). In contrast, active learning and memory formation is associated with an increase in hippocampal neurogenesis (Gould & Gross, 2002; Shors *et al.*, 2002); indeed, neurogenesis may be critical for trace conditioning (Shors, 2004), discussed earlier (pp. 100, 103). Interestingly, one action of antidepressant drugs is to increase hippocampal neurogenesis and neuronal growth (Blows, 2000; Malberg & Duman, 2003; Castren, 2004). In some cases, though not all, antidepressants are an effective therapy for drug dependence (Hughes *et al.*, 2004; Szerman *et al.*, 2005).

5.3.5.5 Perspectives on preventing and treating addiction

If neurosurgery is not a panacea, then it seems likely that conventional macroeconomic and microeconomic manipulations will remain the mainstay of the prevention and treatment of addiction. Addiction is not an all-or-nothing problem, so focusing only on prevalence (the number of people using a drug) may be inappropriate. A strategy of total harm reduction should also consider ways to reduce the average quantity used and the amount of harm per use (MacCoun, 2003b).

Many neuroscientific addiction theories focus on the way in which drugs change the brain. As Kelley & Berridge (2002) recently noted, drugs may activate the same circuits as natural rewards, perhaps in a more potent manner; they may create new states, such as the motivational state of withdrawal; and they may differentially affect the balance of processes that normally contribute to responding for natural rewards, such as habits, goal-directed actions, and cue-induced motivation. There may be other effects, too. Food makes you full and exercise makes you tired, but not all drugs will satiate you to the same extent (Heyman, 2003). Acute intoxication impairs decision making, so the decision to have the sixth pint of beer may not be made in exactly the same way as the decision to have the first. Chronic use of some drugs may alter the brain so as to impair the ability to make good choices (e.g. Rogers *et al.*, 1999a).

Some forms of brain damage may make people more likely to choose impulsively, maximizing short-term rather than long-term gain (e.g. Cardinal *et al.*, 2001). Future treatment strategies may focus on these effects, attempting to reduce drug consumption and reduce the frequency of relapse. Pharmacological strategies (Altman *et al.*, 1996; O'Brien, 1997) include drug replacement (e.g. methadone, nicotine substitution patches), antagonists to block direct drug effects (e.g. naltrexone), agents that trigger illness if the abused drug is taken (disulfiram, acamprosate), drugs that reduce craving such as DA D3 partial agonists (Pilla *et al.*, 1999) and ondansetron (Johnson *et al.*, 2002), and vaccination (Kantak, 2003). Psychological strategies include cue extinction, cognitive–behavioural therapy, and perhaps erasure of drug-associated memories (Nader, 2003). Neuroscientific advances may contribute to the diagnostic process and the matching of treatments to addicts. Techniques ranging from genetics to functional neuroimaging may become useful as a way of predicting which treatments will work best for an individual patient, and in assessing the likely efficacy of that treatment at preventing relapse before the patient is discharged. Both would be important advances.

Macroeconomic approaches take a different perspective. Once addictive behaviours are recognized to be sensitive to drug price and to the relative value of drugs and other activities, it is clear that many options currently available may be further refined. The UK pursues a policy of prohibition with regard to drugs such as heroin and cocaine, intercepting ~20% of imported drugs (Shaw, 2000) and increasing the street price. In the USA, prohibition is estimated to increase the price of cocaine by a factor of 2–4 and heroin by a factor of 6–19 (Miron, 2003). The UK spends about £1 billion per year on programmes specifically to deal with illegal drugs (UK, 2000), of which £380 million is spent on reducing drug availability and £400 million on treatment. Reducing drug availability increases price, and this reduces demand for illicit drugs (Saffer & Chaloupka, 1995); however, if demand is somewhat inelastic (elasticity $|\varepsilon| < 1$), the total amount spent on drugs increases, leading to a large criminal market (up to $500 billion per year worldwide in 1996: Keh, 1996; Streatfeild, 2001) and health costs from contaminated drugs. Treatment of addicts is cost-effective: the benefits are in health (to the addict), reduced health costs (to the state), and reduced crime and criminal justice costs. In the USA, addiction treatment programs save about $42,000 per treated addict per year in the costs of crime and the criminal justice system (McCollister & French, 2003), compared to about $2,000 saved per addict treated per year in health costs. About 30% of those arrested in the UK are dependent on an illegal drug (Shaw, 2000).

In contrast, the UK policy on nicotine and alcohol is to make them legally available but heavily taxed, in order to reduce consumption, ensure that drugs are uncontaminated (by criminalizing unauthorized supply), and to produce revenue that can be spend to the benefit of addicts (e.g. treatment programmes) or society at large (e.g. health care, education). Arguably, the goal of policymakers should be to maximize the overall benefit to society (Hutcheson, 1725; Hume, 1739-1740; Mill, 1863). Whether legalization or prohibition is preferable may depend on the economics of specific drugs (Clark, 2003), but the legalization-plus-taxation option is seen as strongly preferable by many economists (see Miron & Zwiebel, 1995; Becker & Becker, 1998). In the USA, it has been estimated that legalization would lead to a ~100% increase in heroin consumption and a ~50% increase in cocaine consumption (Saffer & Chaloupka, 1995), but a net benefit of $24 billion per year (Miron & Zwiebel, 1995; Shaw, 2000). Opiates cause about 1,000 deaths per year in England and Wales, and cocaine causes about 80 deaths (Hansard, 17 July 2002). Alcohol misuse is estimated to cost the UK perhaps £20 billion per year, of which up about £1.5 billion is spent by the NHS treating alcohol-related diseases, £6.4 billion represents lost economic productivity, and about £12 billion represents the costs of alcohol-related crime (UK, 2003); estimates of the number of deaths per year in England and Wales attributable to alcohol range from 5,000–40,000 (Hansard, 17 July

2002). In contrast, alcohol taxation generates about £11 billion (Smith, 1999). Cigarette taxes currently generate about £9.5 billion, and the NHS spends £1.5 billion treating smoking-related diseases (Parrott *et al.*, 1998), with about 120,000 deaths per year attributable to smoking in the UK (Hansard, 17 July 2002). Such taxes reduce consumption and the adverse consequences of addiction (Keeler *et al.*, 1993; Madden & Bickel, 1999; Chaloupka *et al.*, 2002; 2003). There are many macroeconomic ways to increase "price", including prohibition (reduced availability, higher financial cost, fear of criminal prosecution), restrictions on sale (availability), bans on public consumption (availability, legal sanction), taxation (financial), and stigmatizing drug users (social).

When treating individual addicts, neuroscientific strategies can also be interpreted in economic terms, allowing their comparison to other macroeconomic strategies. Pharmacological techniques can already reduce the value of specific drugs. For example, methadone treats opiate withdrawal symptoms and reduces the "high" produced by concurrently administered heroin, thus reducing the value of heroin. Heroin prescriptions (Uchtenhagen, 1997) reduce the value of contaminated, street heroin. Nicotine patches treat nicotine withdrawal, reducing the value of nicotine. Disulfiram alters ethanol metabolism temporarily so that ethanol consumption induces illness; thus, disulfiram reduces the value of alcohol. Vaccination against cocaine is being tried at the moment (Kantak, 2003); this reduces the "high" and therefore the value of cocaine. All of these can be seen as self-control tactics, and depend on the choices made by the addict: because the addict would prefer a drug-free lifestyle in the long term, he deliberately adopts a strategy (e.g. taking disulfiram) that reduces the future value of his drug. It is also possible to target the brain's motivational systems directly: thus, chemicals that reduce drug seeking in animals (e.g. Pilla *et al.*, 1999) may be another line of therapy.

Better knowledge of the risks of drug taking could also help reduce the perceived value of drugs (Heyman, 2003), and effective advertising of risk should take advantage of human reasoning biases (Slovic *et al.*, 1982), such as by vivid images of the potential unpleasant outcomes of drug use (BHF, 2004). Taken to the opposite extreme, overestimation of the risks of drug taking may also help some people avoid addiction. A personal theory that cocaine use inevitably leads to full-blown destructive addiction might not be true (Warner *et al.*, 1995; NHSDA, 2001; Heyman, 2003; MacCoun, 2003b), but this belief is a self-control device that may prevent some people taking any cocaine (Ainslie, 2001). Misinformation is clearly not a useful public health strategy, since the credibility of advisers depends upon providing accurate information, but clear and vivid statements of genuine risks are of value.

Finally, the addict pays for drugs with money and therefore forfeits other alternative commodities, and may also forfeit commodities that cannot be bought with money, such as social support. Therefore, other strategies can be used to treat addiction (Rachlin, 2003). For example, making it easier for an addict to obtain substitutes for drugs can be as effective as making it harder for the addict to obtain drugs (Green & Fisher, 2000; McCollister & French, 2003; Rachlin, 2003). Rewarding abstinence directly with money or other tangible rewards also promotes abstinence (Higgins *et al.*, 2002; Heyman, 2003). Finally, addicts can use self-control techniques like precommitment to improve their sensitivity to the long term (Ainslie, 2001).

Neuroscientific research aims to understand the neural mechanisms behind addiction, including the operation of neural systems that mediate normal reinforcement and how they are affected by drugs of abuse. In the long run, this research is likely to identify a series of molecular mechanisms that operate to promote drug taking in the addicted brain. Some will prove to be therapeutic targets, for example to reduce drug craving, and may be useful in the treatment of established addiction. Some potential therapies may be specific to the effects of drugs of abuse, but others will not be—for example, reducing strong

cravings for all reinforcers, not just abused drugs. The potential to erase drug-related memories selectively (Nader, 2003) might be of substantial benefit if it can be translated to clinical practice. Other molecular markers may indicate individual vulnerability to addiction, though it is unlikely that this information will be of much practical use, except to indicate to potential users which drugs might be relatively safe to use and which would be likely to lead to strong addictions. Furthermore, techniques may become available to predict which treatments will be best suited to an individual addict by analysing the patient's genetic makeup or neural responses. Thus the most important policy decision to be made regarding the neuroscience of addiction is how much to spend on research that may lead to treatments, and how much to spend on the treatment of addicts who seek help. However, the overall level of consumption of addictive drugs, and therefore a major component of the harm to society related to such drugs, is determined instead by macroeconomic decisions about drug regulation.

5.4 CONCLUSIONS: NEURAL SYSTEMS INVOLVED IN DELAY AND RISK ASSESSMENT

A number of limbic corticostriatal structures, together with major forebrain neuromodulatory systems, play a role in learning and choice involving delayed and probabilistic rewards. The contribution of these structures is best understood for delayed reward (Figure 55), although recent functional imaging and lesion studies have examined the neuroanatomical basis of choice involving uncertain reward.

To summarize, many structures have been implicated in the processing of delayed and/or probabilistic rewards by correlative studies, including studies of abnormalities in disorders of impulsivity such as ADHD, animal single-cell recording studies, and functional imaging studies in normal humans. Not surprisingly, these include many structures that are known to convey information concerning reward value. Impulsive choice (preference for SS over LL rewards) has been induced by lesions of the AcbC, BLA, OFC, and H; self-controlled choice has been induced by lesions of the OFC and STN. Lesions of PrL/IL and ACC do not appear to affect SS/LL reward preference; lesions of the AcbSh do not affect preference between immediate/uncertain and delayed/certain rewards. Studies examining SS/LL preference with a single pair of reinforcers cannot determine whether impulsive or self-controlled choice is due to changes in delay discounting or changes in reinforcer magnitude sensitivity. There is good evidence that changes in reinforcer magnitude sensitivity are minimal following AcbC lesions, and that AcbC damage increases delay discounting. OFC lesions appear both to enhance delay discounting and alter reinforcer magnitude sensitivity. Quantitative determinations of reinforcer magnitude sensitivity following BLA, STN, and H lesions are lacking, though there is some evidence that H lesions do not affect reward magnitude processing.

Lesions of the AcbC do not only impair choice of delayed rewards, but impair instrumental conditioning specifically when reinforcers are delayed. In contrast, although H lesions produce impulsive choice in rats, to some degree they ameliorate the deleterious effects of delays on instrumental conditioning, possibly by reducing contextual competition.

Other structures may also be involved in delayed reinforcement: in principle, any structure that represents future reinforcers across a delay may contribute to their choice, and exert conditioned reinforcing effects on current behaviour, while any structure that maintains a "memory trace" of responses across a delay may support the reinforcement of those responses. The ventral striatum and OFC exhibit such activity (Schultz *et al.*, 1995; 1998; 2000), but so do other structures including the dorsal striatum (e.g. Schultz *et al.*, 1995), implicated in the reinforcement of stimulus–response habits (see Mishkin *et al.*,

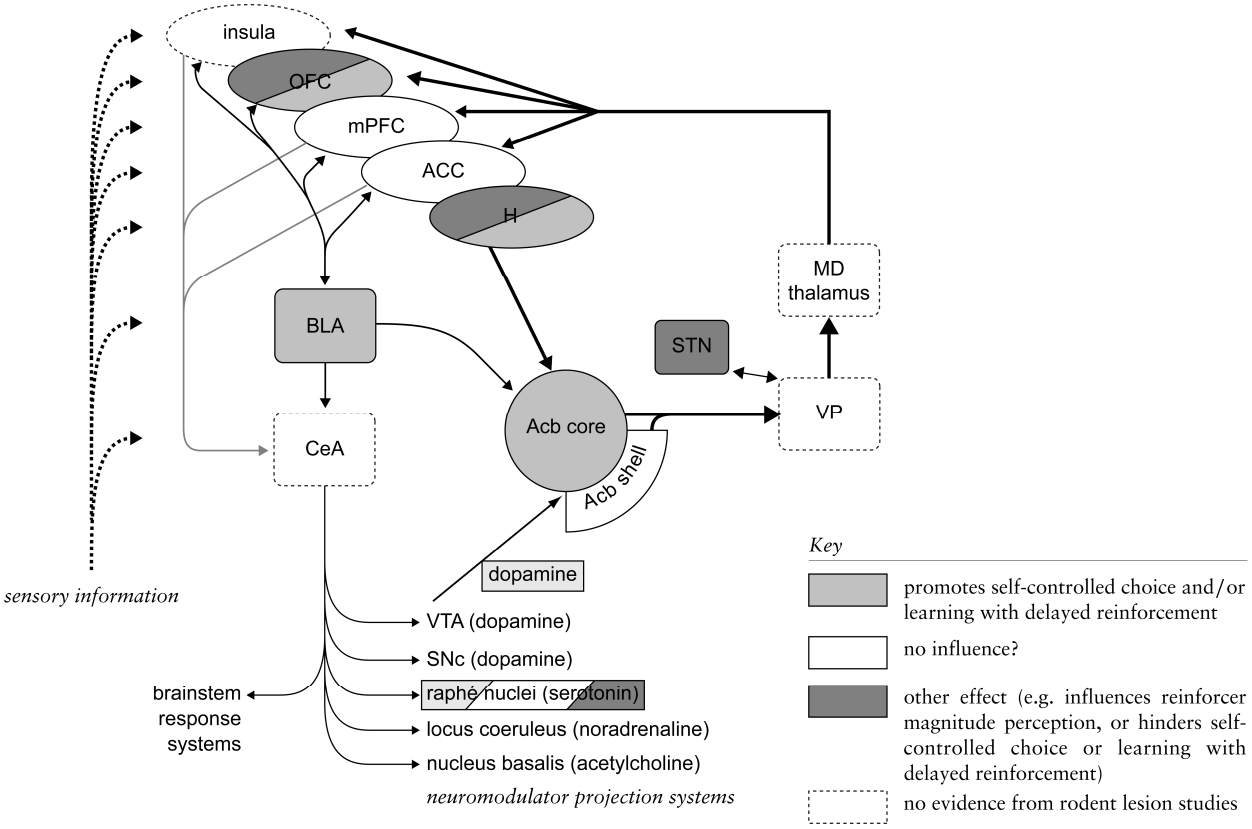

Figure 55: Key limbic corticostriatal structures involved in processing delayed reinforcement

Schematic of the limbic corticostriatal loop, showing key structures (as in Figure 7, p. 21) and their apparent influence on self-controlled choice (ability to tolerate delays to reward) as suggested by lesion studies in the rat. OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex (prelimbic/infralimbic cortex in the rat); ACC, anterior cingulate cortex; H, hippocampal formation; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; Acb, nucleus accumbens; STN, subthalamic nucleus; VP, ventral pallidum; MD, mediodorsal; VTA, ventral tegmental area; SNc, substantia nigra pars compacta. Not all structures and connections are shown; for example, there are projections from prefrontal cortical regions, including the OFC, to the STN (Berendse & Groenewegen, 1991; Maurice *et al.*, 1998; Hamani *et al.*, 2004).

1984; Robbins & Everitt, 1992; Packard & McGaugh, 1996; White, 1997; Parkinson *et al.*, 2000a). Furthermore, the specific pathways of communication required for choice of a delayed reward may be tested: if a structure such as the BLA or hippocampus interacts serially with the AcbC to promote choice of a delayed reward, then a disconnection lesion or inactivation (in which, for example, the BLA is inactivated in one hemisphere and the AcbC is inactivated in the other; see p. 30) should also impair subjects' ability to choose delayed reinforcement.

Neurochemically, DA D_2 receptors have been shown to promote self-controlled choice, in that D_2 antagonists have the opposite effect. NA blockade appears to affect decision making under uncertainty by reducing loss magnitude discrimination when loss probabilities are high. Forebrain 5-HT also appears to promote self-controlled choice, in that a number of studies have shown impulsive choice following 5-HT depletion or antagonists. However, not all studies have found this effect, the role of 5-HT receptor subtypes and chronic adaptations of this system is complex, and 5-HT interacts with other neuromodulators, including DA. Forebrain 5-HT depletion does not appear to alter reinforcer magnitude discrimination.

Fewer interventional studies have looked at the structures required to choose or learn from uncertain rewards, though AcbC and OFC lesions both appear to make rats less willing to choose large, uncertain rewards over small, certain rewards. 5-HT does not appear to affect choice between small, certain and

large, uncertain rewards. Human imaging studies have implicated a number of regions in decisions involving risk, including parts of the medial PFC, the Acb, and the insula. Finally, ACC lesions, BLA lesions, and ACC–BLA disconnection all appear to make rats lazy, in the sense of being less willing to choose large rewards requiring high effort to obtain, when a smaller but low-effort alternative is available.

These studies provide some insight into the pathways through which reward-related information is processed, and suggest underlying neurobiological deficits that may contribute to disorders involving risk taking and impulsive choice. Further considerations apply to drug addiction, since drugs of abuse can produce chronic adaptations in brain regions including the Acb (see Koob *et al.*, 1998b). Human addiction is associated with steep temporal discounting, particularly for the abused drug, and deficits in decision making under uncertainty. Chronic use of psychostimulants has been shown to increase impulsive choice in animal models. One mechanism contributing to addiction may therefore be the ability of drugs of abuse to induce damage or dysfunction in structures that normally promote self-controlled choice, further promoting subsequent impulsive choice and future drug taking. However, we do not yet have a mechanistic description of the way in which delays and probabilities have their effects or are encoded, or the ways in which these various limbic corticostriatal structures interact with each other to enable an animal to choose wisely.