H.B.M. Uylings, C.G. Van Eden, J.P.C. De Bruin, M.G.P. Feenstra and C.M.A. Pennartz
Progress in Brain Research, Vol 126

CHAPTER 17

Limbic cortical–ventral striatal systems underlying appetitive conditioning

John A. Parkinson[1], Rudolf N. Cardinal and Barry J. Everitt*

Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK

Introduction

The neostriatum has a complex structure interpolated within a number of functionally segregated cortico-striato-pallido-thalamic circuits, or loops, which subserve various forms of cognitive, motor and affective functions (Alexander et al., 1986; Alexander and Crutcher, 1990). Alexander and Crutcher (1990) argued that information originating in the cortex passes through the striatum and pallidum before either accessing motor output structures, through the brainstem, or being relayed via the thalamus back to the cortex (particularly the prefrontal cortex). Such loops appear to have wide areas of cortical origin and more focused areas of cortical termination. Earlier, Kemp and Powell (1971) had speculated that cortical information was funnelled through the striatum en masse enabling different processes to be carried out at varying levels of the neural hierarchy. Mounting evidence supports the segregation of these circuits (with a degree of funnelling but only within each segregated domain), with a potential role for dopamine in '... maintaining this segregation, aiding the independent action of striato-pallidal modules' (Bergman et al., 1998).

Within this scheme the region of the ventral striatum termed the nucleus accumbens (NAcc) shows marked heterogeneity both morphologically and in terms of its anatomical connectivity (see Zahm and Brog, 1992). In general terms, the NAcc is a component of 'affective' corticostriatal circuitry (Alexander et al., 1986) receiving major afferent projections from proisocortical areas such as the anterior cingulate cortex (Ant Cing) and orbitofrontal cortex, allocortical areas including the hippocampal formation, and from the basolateral amygdala, a quasi-cortical structure (Carlsen and Heimer, 1986). Whilst these afferents show a degree of preferential targeting across the two subdivisions of the NAcc (core and shell; Zaborszky et al., 1985), the pattern of efferent projections shows a more marked divergence. The core subregion is the more typically striatal, projecting to the ventral pallidum, whereas the shell projects not only to the ventral pallidum but also to the lateral hypothalamus and bed nucleus of the stria terminalis (Heimer et al., 1997). Such differences have led to the proposition that the NAcc shell is a transitional structure, part striatal and part 'extended amygdala', given the morphological characteristics it shares with the central nucleus of the amygdala (CeN) and its extension through the basal forebrain (Alheid and Heimer, 1988; Zahm et al., 1999).

The focus of this chapter is to describe the results of our own and other experiments involving excitotoxic lesions of different nodes of this circuit, in an attempt to understand the functions of corticostriatal loops involving the NAcc and asso-

[1]Present address: Department of Anatomy, University of Cambridge, Cambridge CB2 3DY, UK
*Corresponding author: Tel.: +44 1223-333583; Fax: +44 1223-333564; e-mail: bje10@cus.cam.ac.uk

ciated limbic circuitry that are implicated in reward and motivational processes (Mogenson et al., 1980).

Pavlovian conditioning is one mechanism through which animals learn the nature of relationships between events in the environment. If these relationships are of biological significance then responses already present in an animal's behavioural repertoire (unconditioned responses; UR) can be mapped onto learned predictors (leading to conditioned responses; CR). However, the animal can also take a more active role in learning, in which its acts are instrumental in producing outcomes (instrumental, or operant, conditioning). This behaviour can be flexible and goal-directed (action–outcome learning; A–O) but can also become insensitive to changing contingencies (stimulus–response; S–R habits), a situation often engendered by overtraining or a lack of knowledge regarding the instrumental contingencies (Dickinson, 1985). Whilst habits are inflexible and difficult to extinguish, they do not require declarative knowledge of the instrumental contingencies and their mechanistic, procedural nature 'frees up' processing to allow learning of new contingencies (Adams, 1982). Finally, Pavlovian and instrumental conditioning are not independent or mutually exclusive learning mechanisms (Konorski and Miller, 1937; Rescorla and Solomon, 1967; Mackintosh, 1974). For example, animals will make instrumental responses for Pavlovian cues (conditioned reinforcement); seemingly instrumental responses can be governed by Pavlovian mechanisms (as in discriminated approach) and Pavlovian cues can influence the vigour and direction of instrumental responses (Pavlovian to instrumental transfer). Whilst Pavlovian and instrumental conditioning interact in many learning situations, it is clearly of use to attempt to isolate these forms of learning, as they may be subserved by dissociable neural systems that are normally recruited in parallel to allow integrated adaptive responses to environmental events.

Experimental approach

In the studies summarized here, therefore, we have investigated the effects of manipulations to the NAcc core and shell and anterior cingulate cortex (Ant Cing, which we define here as the rostral portion of Area 24; an agranular subdivision of medial frontal cortex), as well as the central nucleus (CeN) and basolateral area (BLA) of the amygdala and the dorsal and ventral subiculum (Sub), on a number of theoretically well understood animal learning paradigms.

Appetitive Pavlovian conditioning and autoshaping

Pavlovian conditioning is a fundamental learning mechanism that allows an animal to predict and adapt to future events based on previous experience. Limbic structures such as the cingulate cortex have long been implicated in emotional learning (Buchanan and Powell, 1982; Gabriel, 1990; Fredrikson et al., 1995), as have the hippocampal formation (Selden et al., 1991; Moser et al., 1993; Maren et al., 1997) and the amygdala, in both fearful (Hitchcock and Davis, 1986; Selden et al., 1991; Phillips and LeDoux, 1992; Killcross et al., 1997) and appetitive settings (Weiskrantz, 1956; Everitt and Robbins, 1992; Gallagher and Chiba, 1996). The role of the ventral striatum is less well known, though changes in NAcc dopamine release have been documented during both appetitive and aversive Pavlovian conditioning (Di Ciano et al., 1998; Wilkinson et al., 1998). Limbic cortical and ventral striatal structures may therefore interact and be differentially involved in associative learning that underlies motivational and emotional influences on behaviour.

Initially, we focus on an 'autoshaping' procedure, which provides a simple and quantifiable measure of appetitive Pavlovian conditioning relatively unconfounded by other forms of learning, in order to investigate the process by which environmental stimuli are associated with primary reward and thereby gain motivational or emotional valence. Autoshaping was first described in pigeons, who came to approach and peck a key light that had been presented in temporal contiguity with food reward, before approaching and eating the food (Brown and Jenkins, 1968). Regardless of whether there was a contingency between the animals' behaviour and presentation of reward, the

pigeons reliably approached and pecked the key-light stimulus. This approach behaviour has subsequently been interpreted as a Pavlovian sign-tracking response (Hearst and Jenkins, 1974) as it lacks the flexibility and goal-directed nature of instrumental actions (Williams and Williams, 1969). Autoshaping is unlikely to be subserved by the development of an instrumental (S–R) habit, as habits take many more trials to be established than were presented in the autoshaping experiments described here (for example, habits predominate following 500 reinforced trials, but not 100; Adams, 1982). Furthermore, autoshaping can even be acquired using an omission procedure which explicitly prevents any instrumental contingency between response and reinforcement (Williams and Williams, 1969). Autoshaping is produced by the Pavlovian association of the stimulus (subsequently conditioned stimulus; CS) and reward (unconditioned stimulus; US) and has been observed in rats, monkeys, children and adult humans (Sidman and Fletcher, 1968; Zeiler, 1972; Wilcove and Miller, 1974; Boakes, 1977). Figure 1A illustrates the typical acquisition of discriminated autoshaping within our appetitive approach task.

Bilateral excitotoxic lesions of the Ant Cing, but not posterior cingulate or medial prefrontal (including prelimbic and infralimbic) cortex, have been shown to impair autoshaping (Bussey et al., 1997a) (in a manner illustrated in Fig. 1B) and other measures of stimulus–reinforcer learning (Bussey et al., 1997b). (Whilst stimulus–*reward* is a more widely used term, in this review we wish to discuss both appetitive and aversive reinforcers.) Impairments following cingulate cortex lesions are also seen in aversive contexts: both electrophysiological and lesion studies implicate the Ant Cing in the early stages of avoidance learning (Gabriel et al., 1991a; Freeman et al., 1996). Support for the hypothesis that the Ant Cing underlies stimulus–reinforcer learning comes from the finding that Ant Cing lesions actually *enhance* the acquisition of a conditional visual discrimination (Bussey et al., 1996). Such a discrimination can be more effectively learnt via a stimulus–response habit, which might develop in parallel to stimulus–reinforcer associations (presumably in a separate neural system) and potentially conflict with them. Damage to the stimulus–reinforcer learning system would allow the stimulus–response habit system to predominate, resulting in enhanced learning, as was found after Ant Cing lesions by Bussey et al. (1996).

The Ant Cing may gain access to behavioural output through the striatum, a hypothesis that leads to the prediction that lesions to the NAcc, the major recipient of corticostriatal fibres from the Ant Cing, should also impair autoshaping. Indeed, we have found that lesions of the NAcc core markedly impair autoshaping behaviour (illustrated in Fig. 1C), whereas NAcc shell lesions were without effect (as in Fig. 1A), thereby revealing a dissociation in the involvement of NAcc subregions in appetitive Pavlovian conditioning. NAcc core

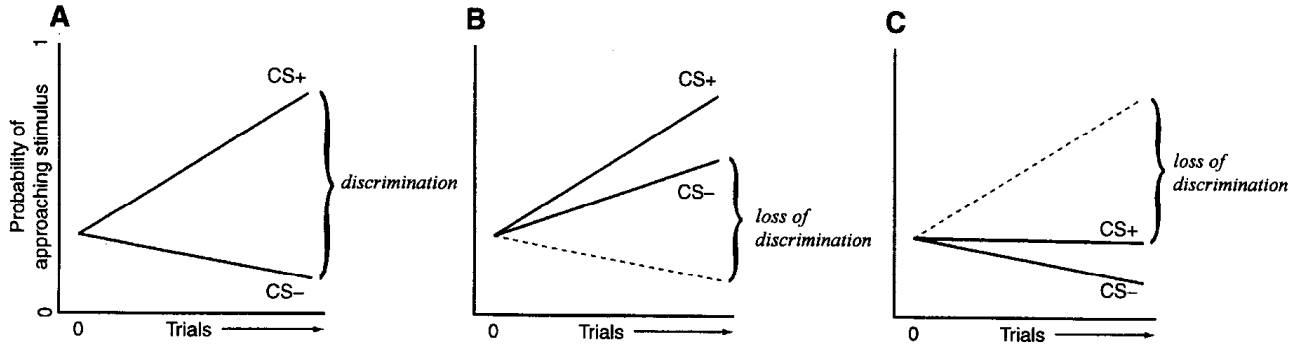

Fig. 1. Autoshaping. (A) shows the phenomenon of autoshaping in normal animals, who come to approach the CS+ and not the CS− following Pavlovian conditioning in which a CS+ is paired with food reward, but the CS− is not. (B) illustrates a loss of discrimination due to an increase in approaches to the CS−; this pattern is typically seen following lesions of anterior cingulate cortex. (C) also illustrates a loss of discrimination, but this time due to a reduction in the frequency of approaches to the CS+, as is seen following lesions of the NAcc core or central nucleus of the amygdala.

lesions significantly reduced the number of approaches that animals made to the CS+, whilst not affecting CS–approaches. These same lesions also impaired conditioned suppression (the reduction in licking from a water tube during the presentation of a CS previously paired with footshock; Parkinson et al., 1999b), an aversive but theoretically similar form of Pavlovian conditioning, suggesting a general role for the NAcc core in such conditioning mechanisms. Lesions of the dorsal striatum, some areas of which also receive cingulate cortex input, do not prevent animals from developing discriminative autoshaped approach responses (Robbins et al., 1997), narrowing the region of interest to the ventral striatum.

If the Ant Cing and NAcc core operate as part of a corticostriatal circuit underlying specific aspects of Pavlovian conditioning, a strong prediction is that a disconnection of the two structures should also impair autoshaping. We have tested this hypothesis by performing a unilateral cingulate cortical lesion and a NAcc core lesion on the contralateral side of the brain; only if the two structures operate in a serial functional manner should a deficit be seen. These disconnection lesions significantly impaired approach behaviour (the loss of discrimination was characterized by both an increase in CS− approaches and a decrease in CS+ approaches, a combination of Fig. 1B, 1C), though single unilateral lesions of either structure did not impair the acquisition of autoshaping (Parkinson et al., 2000b). Similarities in the selective effects of manipulations of prefrontal cortical areas and their striatal projection targets have previously provided evidence for parallel and distinct corticostriatal circuits involving the dorsal striatum (Divac et al., 1967; Divac, 1972; Rosvold, 1972; Dunnett and Iversen, 1980, 1981). The Ant Cing–NAcc core disconnection provides evidence for such interactions involving subdomains of the ventral striatum. Further, the deficits following bilateral Ant Cing and bilateral NAcc core lesions differed, supporting the contention that the cortical and striatal nodes subserve different processes. This also suggests that such a corticostriatal circuit does not operate in isolation, but is influenced by other neural processes at different levels of the circuit, such as the major influence of dopamine (DA) specifically at the level of the striatum, or the hypothesized spiralling influence of corticostriatal circuits on each other (Haber and McFarland, 1999).

The Ant Cing is not the only limbic cortical structure projecting to the NAcc that has been implicated in Pavlovian conditioning. We also investigated the effects of dorsal and ventral Sub lesions on the autoshaping task, and found that they had no effect. Although the hippocampal formation may play a role in Pavlovian conditioning, lesions of the hippocampus or subiculum only appear to affect conditioning to contextual or spatial cues (Selden et al., 1991; Kim et al., 1993). If the hippocampal formation is involved in processing cue configurations that comprise a contextual or spatial CS, to be associated with the unconditioned stimulus elsewhere, the lack of effect of subiculum lesions on autoshaping to discrete cues is not surprising.

Bilateral excitotoxic lesions of the BLA were also without effect on the acquisition of autoshaping. In contrast, CeN lesions significantly impaired autoshaped behaviour by selectively reducing the number of CS+ approaches (illustrated by Fig. 1C) (Parkinson et al., 2000a). This pattern of results mirrors earlier data with an aversive reinforcer: CeN lesions impaired conditioned suppression whilst BLA lesions did not (Killcross et al., 1997). The BLA *is* implicated in emotional learning, though its involvement may be with more complex representations or more flexible outputs than the reflexive stimulus-response evocation of a Pavlovian conditioned response (Hatfield et al., 1996; Everitt et al., in press). However, lesions of the CeN consistently affect Pavlovian conditioning, in both appetitive (Gallagher et al., 1990; Lagowska and Fonberg, 1975; Roozendaal et al., 1990) and aversive (Davis et al., 1997) settings.

What is not immediately clear is how CeN manipulations affect processing in the limbic cortico-striatal circuit, as it is the BLA and not the CeN that projects directly to the NAcc. Nor can recent formulations of the extended amygdala hypothesis easily account for the data, as it is the NAcc shell, not the core, that shares morphological and anatomical features with the CeN (Alheid et al., 1995); our data suggest functional interactions

between the CeN and NAcc core, rather than the shell. However, the CeN may interact with the striatum indirectly through its projections to the chemically defined neurons of the isodendritic core, as there are substantial projections from the CeN to dopaminergic, cholinergic, serotonergic and noradrenergic cell bodies (Davis, 1992; Zahm et al., 1999) of these ascending arousal systems. Several findings are consistent with such a hypothesis; for example, dopaminergic lesions of the CeN or infusions of dopamine receptor antagonists into the amygdala have marked effects upon extracellular dopamine levels in the NAcc (Louilot et al., 1985; Simon et al., 1988; Caine et al., 1995; Hurd et al., 1997). Further, disconnecting the CeN from the dopaminergic innervation of the dorsal striatum impairs conditioned orienting, whilst disconnecting the CeN from the cholinergic innervation of the cortex impairs conditioned attentional mechanisms (Han et al., 1997, 1999). In fact, we have also found that dopaminergic lesions of the NAcc result in impairments in autoshaping (Everitt et al., 1999) much like the effects of excitotoxic NAcc core and excitotoxic CeN lesions. Taken together, these results suggest that a distributed corticostriatal network underlies autoshaping behaviour, and perhaps more generally subserves aspects of appetitive Pavlovian conditioning (illustrated in Fig. 2 and discussed in more detail below).

Conditioned reinforcement and the acquisition of a new response

Stimuli that have been associated with a reinforcer will come to elicit the response produced by the reinforcer. This description of Pavlovian conditioning expresses the learning as a mechanistic form of stimulus–response behaviour ('if a bell rings, then salivate'). It does not necessarily assume that a more complex affective representation of the stimulus has been acquired. However, it is likely that in parallel to a mechanistic form of associative learning, an organism will develop a representation of the value of the predicted outcome ('the bell predicts cheese; cheese is delicious; therefore salivate') (see Dickinson, 1980[1]). Stimuli that have acquired such value will act as conditioned reinforcers and support goal-directed instrumental actions. Thus, Pavlovian conditioned stimuli not only elicit behavioural arousal and approach responses but, by acquiring some of the properties of a goal, gain motivational salience and thereby control instrumental behaviour as conditioned reinforcers (see Mackintosh, 1974).

We have studied this by using a task that isolates the conditioned reinforcement process, namely the acquisition of a new response (Mackintosh, 1974; Hyde, 1976; Robbins, 1978). Initially, a neutral stimulus is paired with the delivery of a primary reinforcer, and the development of conditioning assessed by measuring discriminated magazine approach during presentation of the CS. Subsequently, two novel levers enter the testing chamber. Responding on one (CRf lever) leads to the presentation of the CS, whilst responding on the other (NCRf lever) has no programmed consequence and acts as a control. Testing is carried out in extinction, thus removing any influence of primary reinforcement. The acquired motivational valence of the CS that enables it to act as a conditioned reinforcer is therefore assessed by its ability to reinforce the acquisition of this novel response. Responding with conditioned reinforcement is potentiated by systemic (Hill, 1970) or intra-NAcc (Taylor and Robbins, 1984) administration of d-amphetamine, having behavioural, anatomical and neurochemical specificity for the dopaminergic innervation of the NAcc (Taylor and Robbins, 1986; Cador et al., 1989; Wolterink et al., 1993). However, the control over behaviour by conditioned reinforcement itself does not depend on NAcc dopamine; extensive DA depletion of the

[1]As Dickinson notes, whilst an instrumental habit needs only a simple teaching signal to strengthen the association of stimulus and response (as in procedural learning), more complex forms of behaviour such as goal-directed actions require a semantic (declarative) representation of the goal, including an affective representation of the reinforcer. There is theoretical (Dickinson, 1980; Squire, 1986), behavioural (Dickinson and Balleine, 1994) and neuroscientific (Bussey et al., 1996) evidence to support such a dichotomy in both behaviour and the psychological mechanisms subserving it.

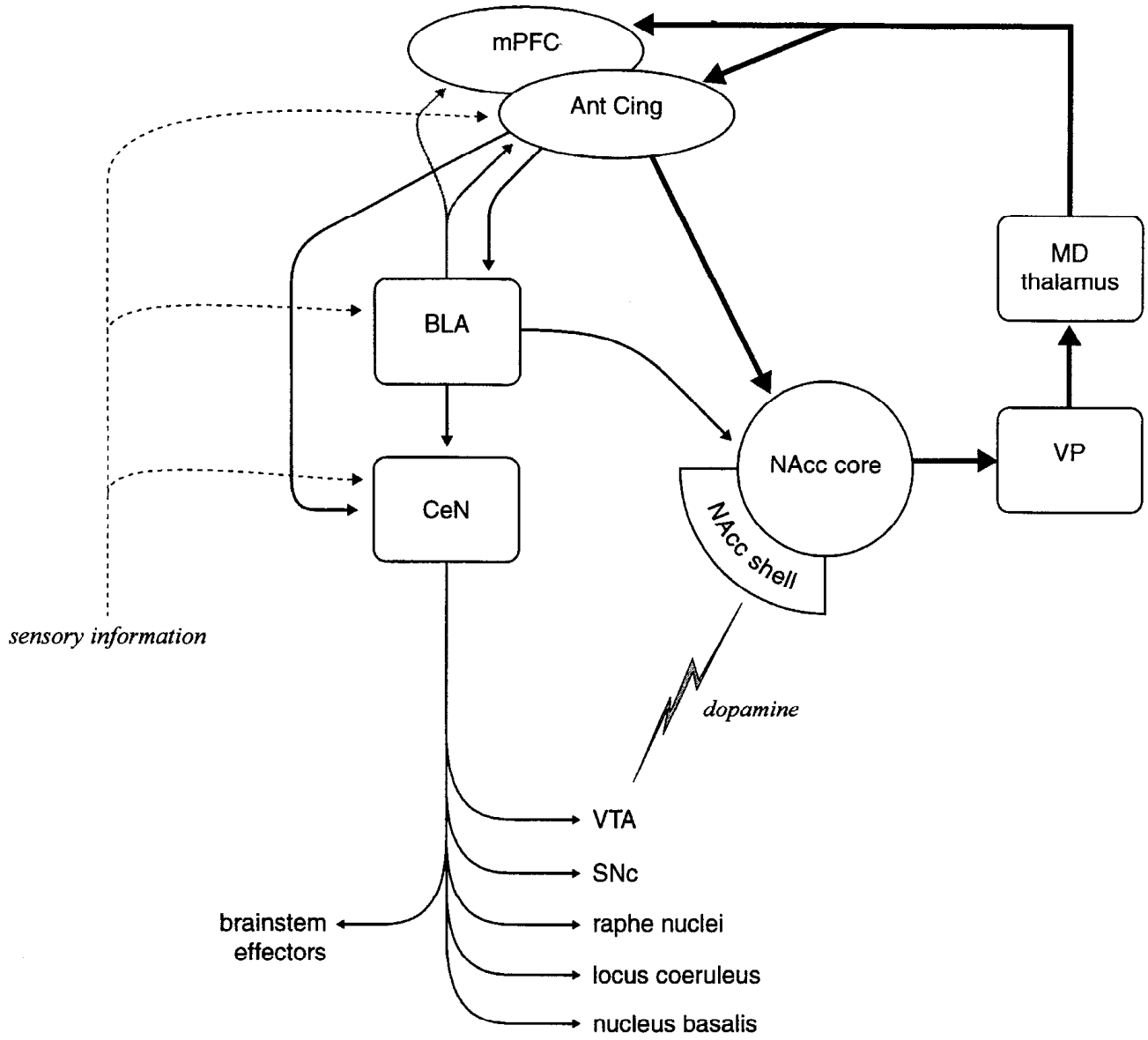

Fig. 2. The limbic corticostriatal loop. The main loop is shown in bold, together with amygdalar structures that contribute to its function in the context of appetitive approach behaviour, conditioned reinforcement and its potentiation by psychomotor stimulant drugs. For clarity, hippocampal structures are not shown. Whilst a functional connection between the anterior cingulate cortex (Ant Cing) and the nucleus accumbens (NAcc) core is necessary for discriminated Pavlovian approach behaviour, the basolateral amygdala (BLA) is critical for conditioned reinforcement. Both Pavlovian approach behaviour and the potentiation of conditioned reinforcement by psychostimulants require the central nucleus of the amygdala (CeN) and dopaminergic innervation of the NAcc; the NAcc shell is the critical site of this potentiation, whilst the NAcc core may be the critical locus for the potentiation of behaviour by the arousing or motivating effects of a Pavlovian CS. The integrity of the medial prefrontal or prelimbic cortex (mPFC) may be required for the detection of instrumental contingencies, and the heavy projection from the BLA to these areas of prefrontal cortex may contribute to the process by which instrumental actions are directed towards appropriate goals.

NAcc or general dopamine receptor blockade within the NAcc does not prevent rats acquiring a new instrumental response with conditioned reinforcement (Taylor and Robbins, 1986; Wolterink et al., 1993). Whilst dopamine may act to gain-amplify or potentiate behavioural responding, reward-related information regarding conditioned reinforcers is presumably derived from limbic

afferents to the NAcc (Burns et al., 1993). Figure 3A illustrates the behaviour of control rats acquiring a new response with conditioned reinforcement.

We have investigated the effects on this task of manipulations of limbic-cortical afferents to the NAcc that are likely sources of affective and sensory information about environmental stimuli, namely the BLA, CeN, hippocampal formation and medial prefrontal (prelimbic) cortex (Cador et al., 1989; Burns et al., 1993; Robledo et al., 1996). Whilst lesions of the prelimbic cortex were without significant effects on this task, lesions of the amygdala and subiculum had marked and different effects on responding with conditioned reinforcement. Lesions of the ventral Sub did not impair Pavlovian or instrumental conditioning, as measured by either stage of the procedure. However, they blocked the ability of intra-NAcc amphetamine to potentiate instrumental responding for the conditioned reinforcer (illustrated in Fig. 3B). The glutamatergic projections from the ventral Sub to the striatum may therefore modulate the potentiative effects of DA at the level of the striatum. Lesions of the BLA impaired the ability of the conditioned reinforcer to support the acquisition of a new response: lesioned subjects failed to respond selectively on the CRf lever, though intra-NAcc amphetamine still potentiated responding (illustrated in Fig. 3C). BLA-lesioned rats were not significantly impaired at magazine approach during the Pavlovian stage of the experiment (Cador et al., 1989), consistent with the lack of effect of BLA lesions on autoshaping. Further, BLA lesions do not impair instrumental responding per se (Burns et al., 1993) or responding on habit-based instrumental tasks (Burns et al., 1999). Impairments following BLA lesions therefore appear to depend on whether the behaviour requires a conditioned representation of the reinforcer to perform the task (Everitt and Robbins, 1992; Gallagher and Chiba, 1996; Gewirtz and Davis, 1997). In contrast, lesions of the CeN did not impair responding with conditioned reinforcement. However, whilst animals with these lesions responded selectively on the CRf lever, the potentiative effects of intra-NAcc amphetamine were completely abolished (much like the effects of ventral Sub lesions and illustrated in Fig. 3B).

To summarize, the BLA, CeN and ventral Sub are all involved in conditioned reinforcement and its potentiation by the mesolimbic dopamine system but their roles are clearly dissociable: (1) the BLA subserves a process by which affective

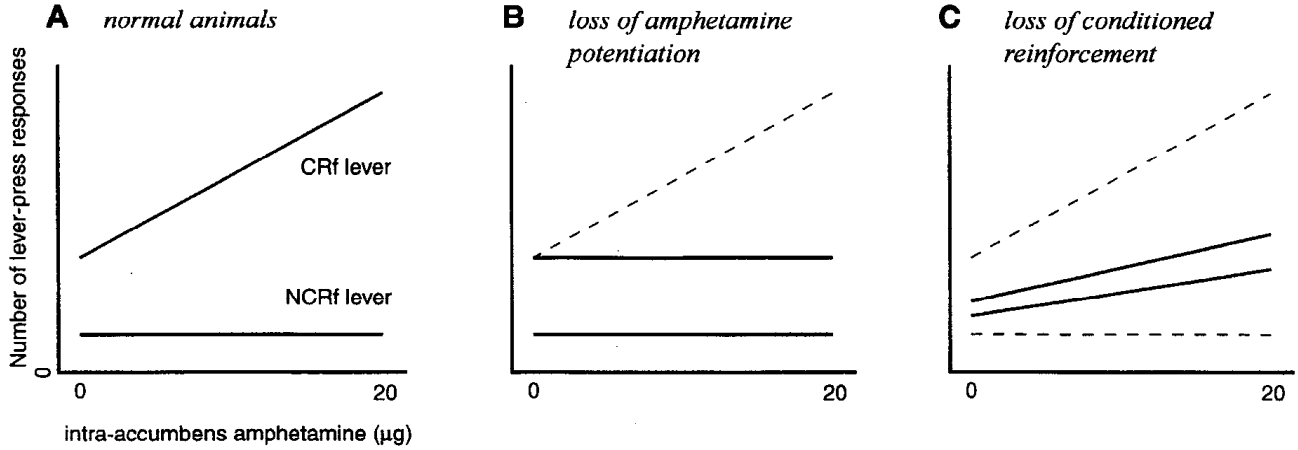

Fig. 3. The acquisition of a new response with conditioned reinforcement. (A) shows the pattern of responding in normal animals. The lever that produces the conditioned reinforcer (CRf lever) supports higher levels of responding than the lever that does not (NCRf lever) under vehicle conditions, and this difference is magnified by intra-accumbens injections of amphetamine. (B) illustrates loss of the potentiative effect of intra-accumbens amphetamine, as observed with lesions of the ventral subiculum, central nucleus of the amygdala, and nucleus accumbens shell. The dotted line represents the control condition, for comparison. In (C), the efficacy of the conditioned reinforcer is reduced but its effect is still potentiated by intra-accumbens amphetamine, as observed following lesions of the basolateral amygdala.

representations of stimuli are used to guide instrumental goal-directed behaviour, and the integrity of this process is fundamental to the conditioned reinforcement effect itself; (2) both the CeN and ventral Sub are essential for the potentiation of conditioned reinforcement by intra-NAcc administration of stimulant drugs, but are not necessary for informational aspects of the conditioned reinforcement process. Whilst the ventral Sub may provide the contextual background upon which the potentiation of conditioned reinforcement depends, the CeN may mediate a motivational influence on responding via the DAergic innervation of the NAcc through its projections to ascending monoaminergic systems.

Recently, we have extended our investigations of the neural basis of conditioned reinforcement in the light of the neuroanatomical demonstration that the NAcc is differentiated into core and shell components, with the caudal NAcc shell resembling the CeN morphologically (the extended amygdala; Alheid et al., 1995). We have found that the potentiative effects of stimulant drugs are dependent on the integrity of the NAcc shell, but not the core (Parkinson et al., 1999a). Selective excitotoxic lesions of the NAcc shell abolish the potentiative effects of stimulants on the conditioned reinforcement process (and attenuate the potentiative effects of stimulants on locomotor activity). However, these same lesions did not interfere with the conditioned reinforcement process. This deficit mirrors that seen following ventral Sub and CeN lesions.

Whilst NAcc shell lesions did not impair learning, core lesions produced a significant retardation of the animals' ability to re-attain criterion levels of the discriminated magazine approach during the first stage of the conditioned reinforcement task. Further, whilst these lesions did not affect conditioned reinforcement under saline (control) conditions, they did interfere with the interaction between conditioned reinforcement and the potentiative effects of amphetamine. Thus, in core-lesioned subjects, intra-NAcc infusions of amphetamine potentiated responding on both the CRf and NCRf levers, much like the effects of BLA lesions on this task. However, the dissociation between the effects, under saline, of core lesions (no impairment) vs. BLA lesions (impairment) suggests that information about conditioned reinforcers from the BLA does not influence goal-directed action solely via the NAcc; it may do so through interactions with other zones of the neostriatum (Viaud and White, 1989; Groenewegen et al., 1990) or with the prefrontal cortex (Balleine and Dickinson, 1998).

One important additional datum extends our current picture of the neural network that underlies conditioned reinforcement and its dopaminergic amplification. This concerns the role of the Ant Cing, implicated in the mnemonic retrieval of stimulus–reinforcer information in the autoshaping task. Lesions of the Ant Cing cortex did not impair temporally discriminated approach to the magazine (in the CRf procedure) or instrumental responding for conditioned reinforcement (Cardinal, Robbins and Everitt, unpublished); nor were the potentiative effects of intra-NAcc amphetamine affected by these lesions. Thus whilst Ant Cing lesions have a marked effect on Pavlovian approach to a CS+ in the autoshaping procedure, they do not appear to impair conditioned reinforcement. We return to this point later.

Synthesis

The concept of corticostriatal circuits has provided a valuable neuroanatomical framework within which to understand the functions of the NAcc and its afferents. The data, summarized in Table 1, offer insights into the nature and function of each structure within this framework and we will now attempt to provide an integrative synthesis of this circuitry.

The anterior cingulate cortex – a role in disambiguating stimuli

The Ant Cing is required for the development of autoshaping; this task also requires the NAcc core, and a functional connection between the two (Parkinson et al., 2000b). Indeed, the Ant Cing is the only major limbic cortical afferent to the NAcc that is required for autoshaping, as lesions of BLA, dorsal or ventral Sub, medial prefrontal cortex or posterior cingulate cortex have no effect on its

TABLE 1

	Ant Cing	NAcc Core	NAcc Shell	Dorsal Sub	Ventral Sub	BLA	CeN
Approach tasks							
Temporally discriminated approach	=	↓	=	=	=	=	=
Autoshaping	↓	↓	=	=	=	=	↓
Potentiation of behaviour							
Intra-NAcc amphetamine potentiation of CRf	=	≠	↓	=	↓	≠	↓
Directed modulation of instrumental behaviour by a conditioned cue							
Conditioned reinforcement	=	=	=	=	=	↓	=

Key: = no difference from shams; ≠ significant interaction; ↓ significant impairment/attenuation relative to shams

acquisition (Parkinson et al., 2000a, b; Bussey et al., 1997a). However, it would be wrong to conclude from the autoshaping deficit that Ant Cing-lesioned animals are entirely unable to acquire Pavlovian associations. Ant Cing lesions did not impair temporally discriminated approach to a CS predictive of food, nor subsequently the ability to acquire a new response using that CS as a conditioned reinforcer, even though the same animals were impaired at autoshaping (Cardinal, Robbins and Everitt, unpublished). Indeed, the neural basis of these tasks has been dissociated before: CeN lesions impair autoshaping (Everitt et al., 1999) but not discriminated approach (Robledo et al., 1996). Therefore, the deficit induced by Ant Cing lesions must be more specific. The discriminated approach task used in the conditioned reinforcement procedure differs from autoshaping in two main ways. Firstly, the autoshaping stimuli are not located at the source of food, whereas the discriminated approach CS is. Secondly, autoshaping involves a discrimination between two stimuli, identical apart from their location, on the basis of their differential association with food. In contrast, the discriminated approach task requires merely that the animal discriminates temporally between the presence and absence of a single predictive stimulus.

The autoshaping deficit observed in Ant Cing-lesioned animals often manifests itself as an increase in responding to the CS− (Bussey et al., 1997a), which might reflect a 'disinhibitory' process or a lack of *discrimination* between the two stimuli. Indeed, Bussey et al. (1997b) showed that Ant Cing-lesioned animals were impaired on an appetitive 8-pair concurrent visual discrimination task. Thus, Ant Cing lesions impair performance on tasks that involve the discrimination of multiple stimuli on the basis of their association with reward. Whether the Ant Cing is itself responsible for the storage of stimulus–reinforcer associations is unclear, but the alternative suggestion that it is involved in attentional processes during learning is made less likely by the demonstration that Ant Cing lesions do not impair accuracy of visual attentional function in rats performing a five-choice serial reaction time task (Muir et al., 1996).

On the basis of the data presented, we speculate that the Ant Cing contributes to a sensory aspect of appetitive conditioning. Without the Ant Cing, animals can learn an affective response to conditioned stimuli; they therefore perform normally in the temporally discriminated approach task. They can also call up an affective representation of the unconditioned stimulus (a role attributed to the BLA; Everitt et al., in press), and so acquire a new response with conditioned reinforcement. However, CS specificity of these representations is impaired; as a result, tasks that depend upon stimulus–reinforcer associations when those stimuli are difficult to discriminate require the Ant Cing (including autoshaping, and 8-pair concurrent visual discrimination). According to this hypothesis, the Ant Cing *disambiguates* the stimulus for the rest of the limbic circuit described, involving the amygdala and NAcc (as illustrated in Fig. 4). This may be a necessary refinement, as the striatum is itself anatomically capable only of discriminating

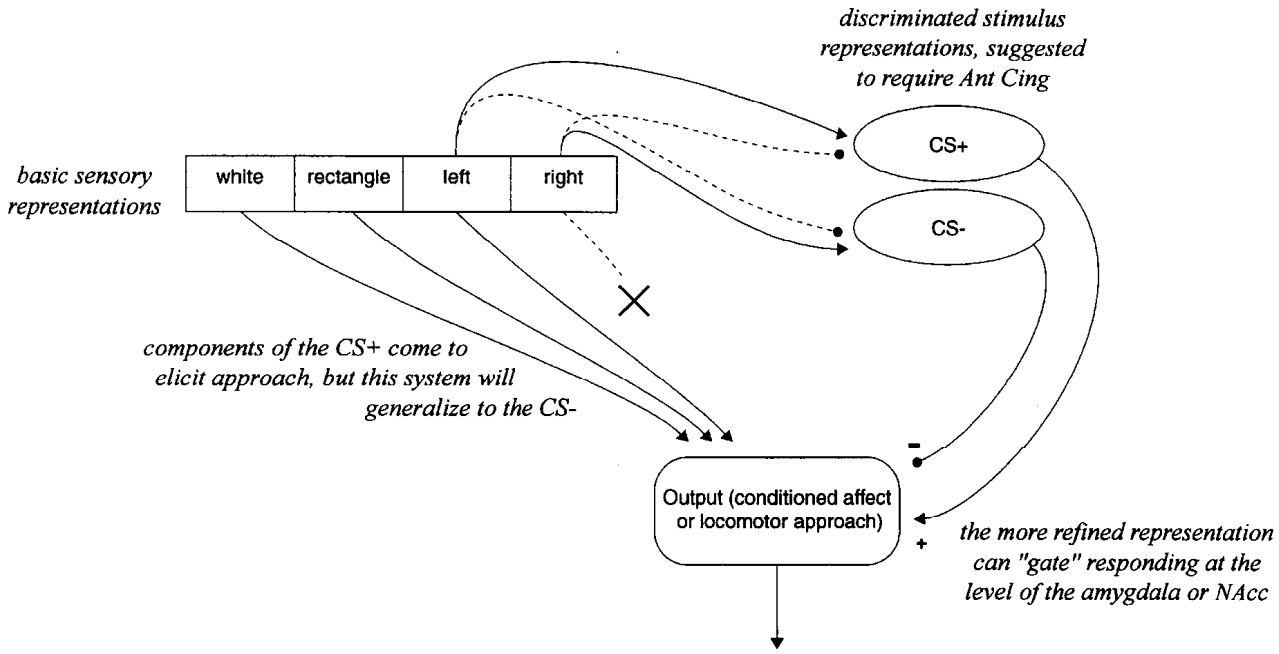

Fig. 4. illustrates 'disambiguation' of stimuli, applied to autoshaping. In this example, the CS+ is a white rectangle on the left and the CS− is an identical stimulus on the right. Expression of autoshaping requires the CeN and NAcc dopamine. In the absence of discriminated activity in the Ant Cing, animals generalize from the CS+ to the CS−, impairing their behavioural discrimination in a disinhibited fashion. However, the animals will still discriminate between the presence and the absence of the CS+.

amongst linearly separable cortical inputs (Wickens and Kötter, 1995, p.206). Furthermore, discrimination of two linearly separable input patterns A and AB where A→reward, AB→0 requires an inhibitory projection from unit B. As the direct cortical inputs to the striatum are all glutamatergic, the striatum would seem unable to solve this discrimination. However, afferents to the NAcc have been shown to gate other glutamatergic inputs (Cools et al., 1991; Pennartz and Kitai, 1991; Floresco et al., 1998) and in this sense, the Ant Cing may operate to control the input of affective information (from the BLA) in order to direct motivational responses to appropriate environmental stimuli. Note that this account of Ant Cing function does not suggest a primary sensory or perceptual role but, more specifically, a role in the retrieval of appropriate affective information for specific stimuli that are attended to and hence in the production of appropriate affective responses to stimuli (see also the recent case study of Turken and Swick, 1999). The concept that even early sensory representations may be neurally dissociated on the basis of the *response* for which the representation is used is not new (Goodale and Milner, 1992); from this perspective, the Ant Cing may be critical for discriminating stimuli *for the purposes of stimulus–reinforcer associations*, but not for other perceptual processes. Ant Cing lesioned animals would be able to discriminate a CS+ from a CS− perceptually, but be unaware as to the correct stimulus towards which appropriate affective responses should be made.

This hypothesis also accounts for the impairment of avoidance learning by Ant Cing lesions in rabbits, shown by Gabriel and colleagues (Gabriel, 1990; Gabriel et al., 1991a, 1991b), for in this task formation of specific stimulus–reinforcer associations confers an advantage. Indeed, in active avoidance behaviour an internally generated expectation of reinforcement may be particularly relevant, as successful behaviour results in the absence of primary reinforcement. These authors have also demonstrated electrophysiologically that in rabbits, the Ant Cing is a site where discriminated activity (discharge to the CS+ but not the CS−) occurs early in discriminated avoidance training (Gabriel and Orona, 1982). More

generally, the Ant Cing may provide stimulus–reinforcer information to other response systems. Thus (as illustrated in Fig. 2) projections from the Ant Cing to the CeN (see Fisk and Wyss, 1997), ultimately influencing brainstem effector mechanisms, may direct autonomic responses toward appropriate environmental stimuli. This is supported by studies demonstrating a role for the Ant Cing in the coordination of autonomic responses (Buchanan and Powell, 1982; Neafsey et al., 1993). More specifically, Powell et al. (1994) demonstrated that Ant Cing lesions disrupted discriminated autonomic responses to a CS+ and CS− whilst not impairing the response itself, much like the effects of Ant Cing lesions on skeletomotor responses in the autoshaping procedure (Bussey et al., 1997a; Parkinson et al., 2000b).

Finally, in tasks where stimulus–reinforcer learning is a disadvantageous strategy, Ant Cing lesions can *improve* performance (Bussey et al., 1996). Ant Cing lesions facilitated learning of a conditional visual discrimination task, as would be expected if the stimulus–reinforcer system were removed and unable to compete with a stimulus–response (habit) system. This preservation of ability may illustrate the segregated functioning of corticostriatal circuits, as the development of stimulus–response habits is believed to be subserved by projections from is neocortex through the caudate nucleus (Reading et al., 1991).

The nucleus accumbens – a role in preparatory behaviour

Many studies have distinguished between behavioural responses on the basis of the temporal distance from behaviour to the ultimate goal. For example, lever-pressing by male rats for access to a female has been doubly dissociated from the unconditioned sexual behaviour (Everitt et al., 1987; Everitt and Stacey, 1987). Such behaviours, temporally distal vs. proximal to the goal, have been described variously as preparatory and consummatory (Blackburn et al., 1987; Robbins and Everitt, 1992), seeking and taking (Arroyo et al., 1998; Everitt et al., 1999), sign tracking and goal tracking (Hearst and Jenkins, 1974), and affective and sensory (Konorski, 1967). Similarly, these two classes of response can be conditioned during associative learning. Konorski (1967) argued that affective responses were general and diffuse and were examples of direct conditioning of central motivational states. In contrast, consummatory responses were precise and reflexive, being directed at the US. Furthermore, affective preparatory responses appear to condition more rapidly and with less constraints on the precise contingency between the CS and US (Mackintosh, 1974) and in this sense may be described as approach/withdrawal responses based on the current motivational state of the animal. Not only is there behavioural evidence to suggest such a distinction between preparatory and consummatory responses (e.g. autoshaping procedures; Terrace, 1981), but recent theories of associative learning have also explicitly encompassed such a dichotomy (e.g. the Affective Extension of Sometimes-Opponent-Process [AESOP] theory; see Wagner and Brandon, 1989). More importantly, separate neural circuits may underlie preparatory and consummatory responses. In a review of the functions of dopamine in the dorsal and ventral striatum, Robbins and Everitt (1992) suggested that the nigrostriatal dopamine system could be characterized as mediating 'sensorimotor co-ordination of consummatory behaviour' whilst the mesolimbic dopamine system 'influences the impact of reward-related stimuli on appetitive [preparatory] aspects of behaviour' (see also Phillips et al., 1991).

Manipulations of the NAcc including 6-OHDA lesions and systemic injections of dopamine receptor antagonists have been shown to reduce the preparatory aspects (including rate of responding) of behaviour directed towards both food and (in male rats) a sexually receptive female, whilst leaving consummatory behaviour unaffected (Blundell et al., 1977; Koob et al., 1978; Kelley and Stinus, 1985; Blackburn et al., 1987; Everitt, 1990). Schedule-induced polydipsia (SIP), a phenomenon whereby excessive drinking is produced by the intermittent presentation of small amounts of food, is also disrupted selectively by 6-OHDA lesions of the NAcc, but not of the dorsal striatum (Robbins and Koob, 1980; Mittleman et al., 1990). NAcc lesions abolish SIP, leaving drinking/ingestion

intact, whilst lesions of the dorsal striatum do not affect SIP but impair the ability of animals to drink effectively. In almost all paradigms studied, manipulations of limbic corticostriatal circuitry affect preparatory but not consummatory behaviour (Robbins and Everitt, 1992). The functional importance of NAcc-dependent preparatory behaviour has also been demonstrated in a naturalistic setting by Whishaw and Kornelsen (1993). Rats normally carry food to a refuge to eat it, and when sated, carry the remaining food to hoard; rats with ibotenic acid or 6-OHDA lesions of NAcc were selectively impaired in this preparatory behaviour, failing to carry food to hoard it. The same rats were not impaired at carrying-to-eat, or eating itself.

Implications for theories of nucleus accumbens function

There are at least three mechanisms that contribute to instrumental behaviour. Firstly, animals may act in a goal-directed fashion (Dickinson and Balleine, 1994); this requires propositional knowledge of the instrumental contingency between actions and outcomes, and a representation of the outcome as a goal. Secondly, animals may act in a habitual, or stimulus–response fashion; this is engendered by overtraining (Adams, 1982; Dickinson et al., 1995). Thirdly, Pavlovian stimuli may modulate the performance of ongoing instrumental behaviour (Lovibond, 1983). Most of these processes are unaffected by NAcc lesions. For example, NAcc lesions do not affect the ability of rats to perceive changes in contingency and adjust their behaviour accordingly (Balleine and Killcross, 1994), though lesions of prelimbic cortex do (Balleine and Dickinson, 1998). Similarly, NAcc lesions leave rats able to detect changes in the goal status of particular foods (Balleine and Killcross, 1994), though the insular cortex may be critical for this representation (Balleine and Dickinson, 1998). Stimulus–response habits also persist following NAcc lesions or dopamine depletion (Robbins et al., 1990; Reading et al., 1991).

However, a number of studies have implicated the NAcc as a critical site for the arousing, or modulatory, influence of Pavlovian appetitive conditioned stimuli on ongoing motor performance, including instrumental behaviour and locomotor approach. This has been demonstrated clearly by Pavlovian-to-instrumental transfer (PIT) experiments. If an animal is trained to press a lever for food and subsequently tested in extinction, presentation of a Pavlovian CS that predicts the same food increases the rate of lever-pressing (an effect first shown by Lovibond, 1983). Lesions of the NAcc core impair the basic PIT effect (Hall et al., 1999), as does systemic treatment with the dopamine receptor antagonist pimozide (Smith and Dickinson, 1998), leading us to speculate that the ability of an appetitive Pavlovian CS to potentiate instrumental behaviour depends on the mesolimbic dopamine system. The PIT effect can be subdivided into a general arousing effect of appetitive Pavlovian stimuli (Dickinson and Dawson, 1987) and a more informational component, by which Pavlovian CSs selectively potentiate instrumental behaviour with which they share an outcome (Colwill and Rescorla, 1988). It remains to be seen whether the arousing (general) and informational (specific) mechanisms by which non-contingent stimuli potentiate behaviour are the same as those involved for contingent stimuli (conditioned reinforcers). In both cases, such evidence as is available suggests that the informational component is subserved by glutamatergic projections from limbic structures, whilst the arousal component is derived from ascending projections from the isodendritic core (Taylor and Robbins, 1984; Cador et al., 1989; Bussey et al., 1997a; Han et al., 1997; Hall et al., 1999).

The role of these motivational processes in performance under different schedules of reinforcement is imprecisely understood. From an economic point of view, there is a high probability of executing an action when the motivation to perform that action exceeds the response costs, which include the work-related costs (effort). Schedule performance depends on these two variables; indeed, the progressive-ratio (PR) schedule is based on these principles. Salamone and colleagues have demonstrated that 6-OHDA-induced dopamine depletion of the NAcc impairs the ability of animals to overcome response costs (Salamone, 1994). Thus, DA-depleted rats will forgo the opportunity to press a lever for a preferred food,

instead consuming more of a less-preferred but freely available food (Salamone et al., 1991; Cousins et al., 1993). Similarly, dopamine depletion impairs responding on high-rate but not on low-rate schedules (McCullough et al., 1993; Salamone et al., 1993; Sokolowski and Salamone, 1998; Aberman and Salamone, 1999). These results are compatible with the loss of a dopaminergic motivational influence that contributes to normal performance. Indeed, NAcc dopamine depletion does not only impair lever-pressing responses in such situations, but also displacement behaviour occurring when food is delivered on a fixed-time schedule (Robbins and Koob, 1980). Such behaviour cannot easily be described as carrying a response cost, whereas it may reflect a potentiation of irrelevant available behaviours by a motivational effect of the food (Robbins and Koob, 1980).

Finally, a wide range of other tasks that depend on the effect of Pavlovian stimuli on instrumental or approach behaviour are also sensitive to lesions of NAcc or its afferents. The level of instrumental lever pressing is reduced by excitotoxic lesions of the NAcc (Balleine and Killcross, 1994), consistent with the loss of a Pavlovian motivational effect that normally potentiates responding. Kelley et al. (1997) have also demonstrated the profound effect of intra-NAcc infusions of glutamate antagonists on Pavlovian and instrumental responding. Bilateral lesions of BLA, or NAcc, or a disconnection of the two, abolish a previously acquired conditioned place preference (CPP) for food (Everitt et al., 1991); similarly, lesions of structures downstream from the NAcc, including the ventral pallidum and mediodorsal thalamus, also impair acquisition of a CPP (McAlonan et al., 1993). The BLA and NAcc are also critical for the acquisition of responding under second-order schedules of sexual or cocaine reinforcement (Everitt et al., 1989; Whitelaw et al., 1996), in which the second-order CS is critical for responding in normal animals (Arroyo et al., 1998). As discussed above, lesions of the anterior cingulate cortex, or NAcc, or a disconnection of the two, impair the acquisition of autoshaping (Bussey et al., 1997a; Parkinson et al., 2000b).

We hypothesize that the Ant Cing–NAcc circuit underlies this motivational arousal, termed affective responding by Konorski (1967) and appetitive or preparatory conditioning by Robbins and Everitt (1992). More specifically, when no stimulus-bound pattern of skeletomotor behaviour is appropriate, such as before a predicted goal arrives, the NAcc may serve to maintain behavioural arousal and prepare the organism for voluntary action. However, in situations where a discrete skeletomotor response is appropriate, such as during habitual responding, or when a goal has been reached and thus consummatory responding is engaged, corticotal circuitry directed through the caudate nucleus may predominate (Reading et al., 1991; Robbins and Everitt, 1992). Finally, the Ant Cing–NAcc circuit may also modulate ongoing behaviour in a manner that depends on the motivational state of the animal and the previous conditioning history of the environment in which the behaviour is being maintained, with the NAcc providing the arousal by which appetitive conditioned stimuli may elicit approach (autoshaping) or potentiate other behaviours (PIT), and the capacity to switch that arousal towards different responses, and the Ant Cing serving to direct the arousal towards the appropriate CS (and away from inappropriate stimuli) in situations where several such stimuli are present.

Implications for theories of corticostriatal function

1. The striatum as a switching device. Over two decades ago, Lyon and Robbins (1975) hypothesized a behavioural switching mechanism based on the dopaminergic innervation of the striatum. This concept has evolved and Redgrave et al. (1999a) reviewed and extended theories of the basal ganglia as a central behavioural switching mechanism (Lyon and Robbins, 1975; Cools, 1980; Dunnett and Iversen, 1982; Jaspers et al., 1984; Redgrave et al., 1999a), which provides a useful framework within which to discuss the present data. According to this theory, the striatum selects responses in the cortical structures to which it is connected, by disinhibiting one 'channel' passing through it, and using a winner-take-all system to ensure that only a single channel is active. Superimposed upon this picture may be a hierarchy: whilst the motor loop of the dorsal striatum switches between incompatible commands to the musculature, the limbic loop may operate at a higher level to switch between different overall behavioural strategies (this con-

cept of hierarchical switching is illustrated in Fig. 5). Such a mechanism would provide an efficient way to resolve conflicts over access to limited motivational, cognitive and motor resources (Redgrave et al., 1999a).

Striatal circuitry is consistent with this hypothesis. Striatal spiny neurons are well suited by their connectivity and electrophysiological properties to act as pattern detectors: they are bistable, receive a highly convergent projection from the cortex and require cortical input to enter the active ('up') state (O'Donnell et al., 1999). They are therefore suited to 'registering' patterns of cortical input (see Houk and Wise, 1995; Wilson, 1995) and appear to do so (Schultz et al., 1995). More controversially, they may receive a 'teaching signal' to influence future cortical pattern recognition, discussed later. A caveat is that the neostriatum is only able to discriminate cortical input patterns that are linearly separable, as it is equivalent to a single-layer network (Wickens and Kötter, 1995), and its discriminative ability is further limited by the fact that direct corticostriatal projections are excitatory, as discussed above. Within the major corticotal loops (skeletomotor, oculomotor, cognitive and limbic), there are parallel channels: circuits that maintain a degree of functional segregation (Alexander et al., 1986) and which may compete for output (Deniau et al., 1982). Striatal output circuitry operates on a disinhibitory principle: GABAergic neurons in the pallidum and substantia nigra pars reticulata tonically inhibit thalamocort-

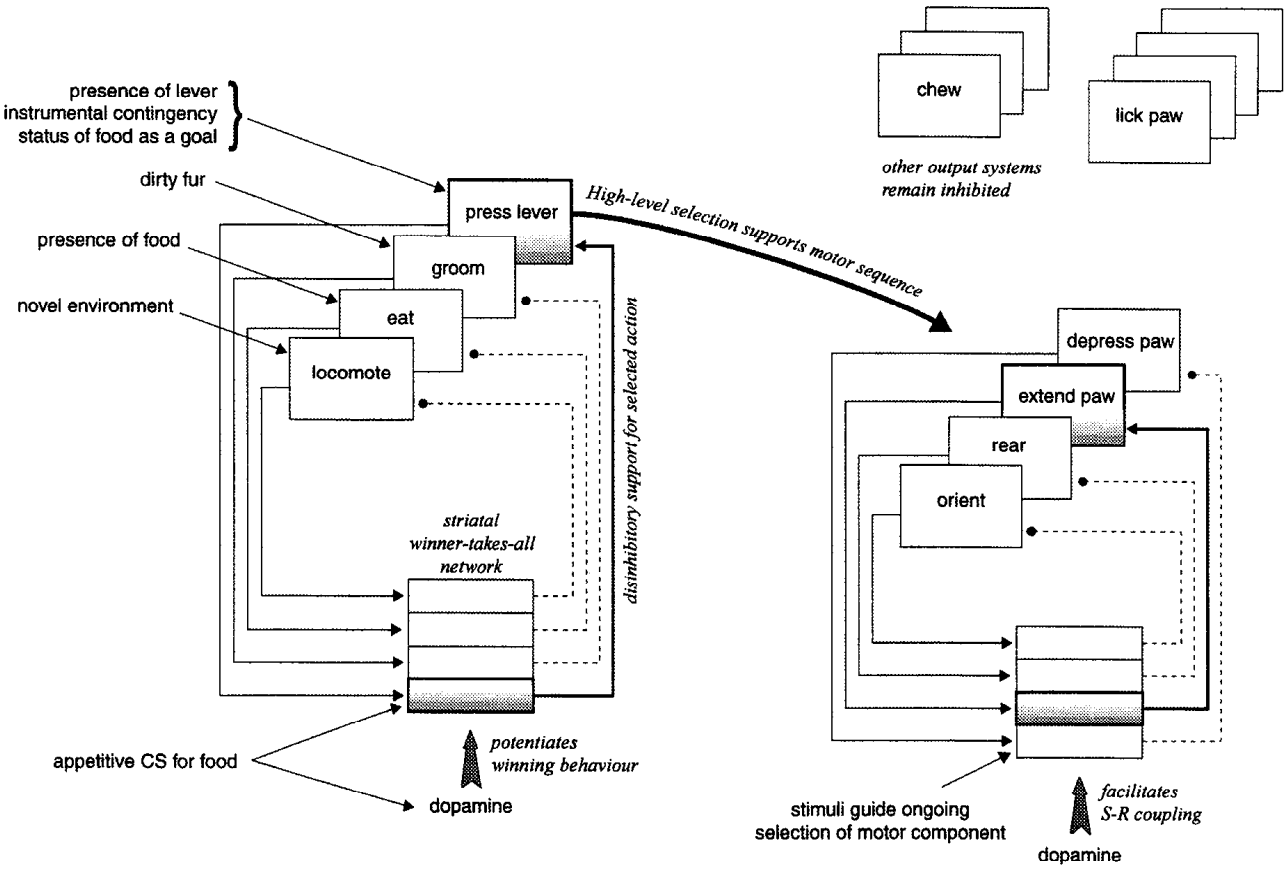

Fig. 5. illustrates concepts of central switching mechanisms and hierarchies of behaviour. The left-hand circuit, representing the limbic corticostriatal loop, influences the selection of complex behaviours on the basis of conditioned motivational stimuli. The right-hand circuit, representing the motor corticostriatal loop, selects motor responses on the basis of environmental stimuli in an S–R fashion. The interaction between the circuits represents the hierarchy of behaviour: motor components can only be selected when they are part of the chosen higher-level behaviour.

ical circuits, and activity in GABAergic striatal neurons can inhibit GP/SNr neurons, disinhibiting the cortex (see Alexander and Crutcher, 1990; Chevalier and Deniau, 1990). This disinhibition does not itself trigger behaviour, but permits it (reviewed by Chevalier and Deniau, 1990), as the striatum does not generate simple behaviour patterns, but chooses and/or links them. Those studies that have explicitly looked at switching are consistent with this hypothesis; thus NAcc lesions have been shown to impair 'strategy switching' in a reversal situation (Reading and Dunnett, 1991), though not on all tasks (Stern and Passingham, 1995).

2. *Acute modulation of striatal function by dopamine.* Whilst glutamatergic afferents to the striatum constitute high-bandwidth pathways, capable of carrying a large amount of information, the dopaminergic input is a low-bandwidth pathway (Schultz, 1994; Mirenowicz and Schultz, 1996; Zoli et al., 1998), consistent with a role in modulating other information passing through the striatum (the functions of striatal dopamine are of necessity entirely constrained by the underlying function of the corticostriatal loops). Direct evidence for such a modulatory role is provided by the conditioned reinforcement paradigm (Taylor and Robbins, 1984): infusion of dopaminergic agonists into NAcc increases the rate (i.e. the probability) of responding for a conditioned reinforcer, but can only 'amplify' this effect of conditioned reinforcers when information about them is arriving via glutamatergic afferents, in this case the BLA (Cador et al., 1989; Burns et al., 1993).

At a cellular level in the striatum, dopamine probably focuses activity by increasing output from the most active medium spiny neurons (which are in the minority) and decreasing output from the less active cells (see Grace, 1987; Wickens and Kötter, 1995). This is mirrored at a behavioural level; increasing doses of dopamine agonists produce higher rates of activity in more and more limited categories of response (Lyon and Robbins, 1975) until stereotypy ensues.

The differences in the functions of dopamine in the dorsal and ventral striatum (reviewed by Robbins and Everitt, 1992) can then be viewed as a common action of dopamine on striatal circuits that switch different aspects of behaviour. In the dorsal striatum, dopamine receptor agonists alter the relative probability of simple motor acts, leading to stereotypy at high doses. Antagonists or dopamine depletion prevent relevant stimuli from eliciting simple motor responses, including consummatory responses; the spectrum is from a slowed response to akinesia. Similarly, dopamine depletion of the dorsal striatum impairs learning and performance of a task based on stimulus–response decision rules (Robbins et al., 1990). As would be predicted from the corticostriatal loop account, cognitive stimulus–response coupling is also impaired by dorsal striatal dopamine depletion (see Robbins et al., 1990). This description emphasizes the role of the striatum as a device that selects behavioural output *in appropriate stimulus situations.*

In the ventral striatum, dopamine receptor agonists and antagonists similarly increase or decrease the probability of stimuli affecting ongoing behaviour, but the behaviour so altered is qualitatively different. The response that is potentiated in the conditioned reinforcement task is a complex motor act, arbitrarily chosen by the experimenter, and induced by a process of conditioned motivation. The ventral striatum also mediates motivational influences on locomotion and on preparatory aspects of behaviour (Robbins and Everitt, 1992). Switching between complex behaviours is itself reduced by dopamine depletion or antagonist injection into the NAcc (Evenden and Carli, 1985; Bakshi and Kelley, 1991).

3. *The striatum and learning.* The question of whether the striatum is involved in learning is controversial. If the switching hypothesis is correct, then striatal learning would manifest itself as a permanent change in the probability of a particular cortical pattern or behaviour being disinhibited by the striatum, given a certain pattern of inputs. Such a mechanism would also be capable of learning motor sequences. A role for the basal ganglia in habit formation was originally suggested by Mishkin et al. (1984), who saw a habit as a direct stimulus–response association that was learned slowly but was stable. Much of the subsequent work on this issue has proved controversial (see

Wise, 1996), and some of the best evidence for a long term change in behaviour that is dependent on the striatum is from an experiment by Packard and McGaugh (1996). They trained rats in a T-maze with one arm consistently baited. This task is soluble by two methods: repeating the reinforced response, or approaching the place where food was found (a 'place response'). These may be distinguished by letting the rat approach the choice point from the opposite direction. After eight days of training, most rats made place responses. Inactivation of the dorsal hippocampus with lidocaine on the test session eliminated this tendency, such that the rats showed neither place nor motor response learning, but inactivation of the dorsolateral caudate nucleus had no effect. After 16 days of training, however, most rats made the motor response that had been reinforced. Inactivating the caudate nucleus eliminated this and reinstated place responding, whilst inactivation of the hippocampus had no effect. Therefore, development of a stimulus to motor response mapping takes place slowly during reinforced training and comes to dominate behaviour, and its performance depends upon the caudate nucleus.

4. Dopaminergic effects on striatal learning. Dopamine has been widely suggested to affect striatal learning. At a cellular level, dopamine can mediate heterosynaptic plasticity in the striatum (reviewed by Wickens and Kötter, 1995): pre- and post-synaptic activity in the corticostriatal pathway produces long-term depression (Calabresi et al., 1992) but phasic dopamine may reverse this, producing a potentiation (Wickens et al., 1996, but see also Pennartz et al., 1993). Based on the response properties of midbrain dopamine neurons, computational neuroscientists have suggested that dopamine acts as a teaching signal for striatal learning (Houk et al., 1995; Montague et al., 1996; Schultz et al., 1997). It would certainly be maladaptive to develop inflexible, habitual behaviour if such learning were not guided by a signal at least correlated with reinforcement, and the dopamine signal fulfils this property.

While the suggestion that dopamine acts as a teaching signal is controversial (e.g. Pennartz, 1995; Redgrave et al., 1999b) – for example, many effects of dopaminergic manipulations are interpretable as effects on attentional processes or response switching – there is some behavioural evidence for dopaminergic consolidation of S–R learning. The 'win-stay' radial maze task may be solved by a stimulus–response rule as approach to an illuminated arm is always rewarded. Performance on this task is also sensitive to caudate lesions (Packard et al., 1989) and improved by post-training injections of dopamine receptor agonists into the caudate nucleus (Packard and White, 1991). These effects are neurally and behaviourally specific: caudate manipulations had no effect on a 'win-shift' task in the same apparatus, and were doubly dissociated from the effects of lesions of the hippocampus or post-training hippocampal injections of dopamine receptor agonists. Post-training microinjections represent a critical experimental test for the demonstration of task consolidation, as they cannot affect task performance. However, the task cannot be characterized as a stimulus–response habit as clearly as the T-maze task.

Does ventral striatal dopamine consolidate learning of a stimulus–motivation mapping in a similar manner? At present, this is an unanswered question. Unpublished observations from our laboratory indicate that rats responding for a conditioned reinforcer in extinction under saline conditions respond more if they have previously responded with intra-accumbens amphetamine, which is contrary to the general tendency for responding to extinguish (Cardinal, Robbins and Everitt, unpublished observations). However, these data are confounded by response generalization effects (the possibility that the rats responded more simply because they have a history of high responding in the same environment). Post-training injections of the dopamine D2 receptor antagonist sulpiride into NAcc have been shown to impair water-maze performance (Setlow and McGaugh, 1998; Setlow and McGaugh, 1999), but the theoretical basis of this task is not clear.

Since the dorsal striatum is involved in the development of stimulus–response habits (Packard and McGaugh, 1996; Reading et al., 1991), whilst the ventral striatum is involved in motivational processes (Robbins and Everitt, 1992), a qualitative difference may exist between the two. However, if

the two structures (at least, the dorsal striatum and the nucleus accumbens core) perform similar functions at a neural level then a direct comparison is fruitful. An S–R habit may be defined as the production of a motor response with a fixed probability given a set of stimuli; that is, a simple and inflexible input/output mapping. Habits are also learned slowly. But if the striatum subserves S–R habits, then the stimulus is whatever cortical inputs arrive at a striatal segment, which depends upon the corticostriatal loop of which it is part, and the response is the pattern that the striatum consequently induces in the structures to which it projects. For the ventral striatum, the equivalent habit would be the inflexible generation of a motivational effect in a particular context.

Such 'motivational habits' may be of critical importance in the phenomenon of drug addiction. Compulsive drug use is characterized by behaviour that is inflexible, for it persists despite considerable cost to the addict, may become dissociated from subjective measures of drug value (Robinson and Berridge, 1993), and may be elicited by specific environmental stimuli (O'Brien et al., 1986); yet it involves complex, goal-directed behaviour for procuring and self-administering a drug. In a behavioural hierarchy, inappropriate reinforcement of low-level behaviours may be of trivial consequence whereas drug-induced reinforcement of a motivational process that has flexible cognitive and motor systems at its disposal may be far more destructive.

The neuroanatomical framework within which corticostriatal circuitry has been discussed in this review supports the early contentions of workers in this field (Alexander et al., 1986). Thus, different zones of the neostriatum carry out qualitatively similar processes within qualitatively different functional circuits. Whilst cortical structures may provide the informational components to behavioural responses, subcortical domains such as the striatum may provide the mechanism by which stimulus configurations are mapped onto appropriate responses.

Acknowledgements

Supported by an MRC Programme Grant (G9537855) to BJE, T.W. Robbins and A. Dickinson. Also supported by an MRC Co-operative in Brain, Behaviour and Neuropsychiatry and in part by a Wellcome Trust grant to TWR and BJE. JAP was supported by a BBSRC research studentship and an Oon Khye Beng Ch'hia Tsio Scholarship. RNC was supported by an MRC research studentship and a James Baird award from the University of Cambridge School of Clinical Medicine.

References

Aberman, J.E. and Salamone, J.D. (1999) Nucleus accumbens dopamine depletions make rats more sensitive to high ratio requirements but do not impair primary food reinforcement. *Neuroscience*, 92: 545–552.

Adams, C.D. (1982) Variations in the sensitivity of instrumental responding to reinforcer devaluation. *Q.J. Exp. Psychol. B.*, 34: 77–98.

Alexander, G.E. and Crutcher, M.D. (1990) Functional architecture of basal ganglia circuits – neural substrates of parallel processing. *Trends Neurosci.*, 13: 266–271.

Alexander, G.E., Delong, M.R. and Strick, P.L. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.*, 9: 357–381.

Alheid, G.F., de Olmos, J.S. and Beltramino, C.A. (1995) Amygdala and Extended Amygdala. In: G. Paxinos (Ed.), *The Rat Nervous System*, Vol. 1, *Forebrain and Midbrain*, Sydney, Academic Press, pp. 495–578.

Alheid, G.F. and Heimer, L. (1988) New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders – the striato-pallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience*, 27: 1–39.

Arroyo, M., Markou, A., Robbins, T.W. and Everitt, B.J. (1998) Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: effects of conditioned cues and continuous access to cocaine. *Psychopharmacology*, 140: 331–344.

Bakshi, V.P. and Kelley, A.E. (1991) Dopaminergic regulation of feeding behavior. 1. Differential effects of haloperidol microinfusion into three striatal subregions. *Psychobiology*, 19: 223–232.

Balleine, B. and Killcross, S. (1994) Effects of ibotenic acid lesions of the nucleus accumbens on instrumental action. *Behav. Brain Res.*, 65: 181–193.

Balleine, B.W. and Dickinson, A. (1998) Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology*, 37: 407–419.

Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M. and Vaadia, E. (1998) Physiological aspects of information processing in the basal ganglia of normal and Parkinsonian primates. *Trends Neurosci.*, 21: 32–38.

Blackburn, J.R., Phillips, A.G. and Fibiger, H.C. (1987) Dopamine and preparatory behavior. 1. Effects of pimozide. *Behav. Neurosci.*, 101: 352–360.

Blundell, J.E., Strupp, B.J. and Latham, C.J. (1977) Pharmacological manipulation of hoarding: further analysis of amphetamine isomers and pimozide. *Physiol. Psychol.*, 5: 462–468.

Boakes, R.A. (1977) Performance on learning to associate a stimulus with positive reinforcement. In: H. Davis and H.M.B. Hurwitz (Eds.), *Operant-Pavlovian Interactions*, Hillsdale, N.J., Erlbaum, pp. 67–97.

Brown, P.L. and Jenkins, H.M. (1968) Auto-shaping of the pigeon's keypeck. *J. Exp. Anal. Behav.*, 11: 1–8.

Buchanan, S.L. and Powell, D.A. (1982) Cingulate cortex – its role in Pavlovian conditioning. *J. Comp. Phys. Psychol.*, 96: 755–774.

Burns, L.H., Robbins, T.W. and Everitt, B.J. (1993) Differential effects of excitotoxic lesions of the basolateral amygdala, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of *d*-amphetamine. *Behav. Brain Res.*, 55: 167–183.

Burns, L.H., Everitt, B.J. and Robbins, T.W. (1999) Effects of excitotoxic lesions of the basolateral amygdala on conditional discrimination learning with primary and conditioned reinforcement. *Behav. Brain Res.*, 100: 123–133.

Bussey, T.J., Everitt, B.J. and Robbins, T.W. (1997a) Dissociable effects of cingulate and medial frontal cortex lesions on stimulus-reward learning using a novel Pavlovian autoshaping procedure for the rat: implications for the neurobiology of emotion. *Behav. Neurosci.*, 111: 908–919.

Bussey, T.J., Muir, J.L., Everitt, B.J. and Robbins T.W. (1996) Dissociable effects of anterior and posterior cingulate cortex lesions on the acquisition of a conditional visual discrimination: facilitation of early learning vs. impairment of late learning. *Behav. Brain Res.*, 82: 45–56.

Bussey, T.J., Muir, J.L., Everitt, B.J. and Robbins, T.W. (1997b) Triple dissociation of anterior cingulate, posterior cingulate, and medial frontal cortices on visual discrimination tasks using a touchscreen testing procedure for the rat. *Behav. Neurosci.*, 111: 920–936.

Cador, M., Robbins, T.W. and Everitt, B.J. (1989) Involvement of the amygdala in stimulus reward associations – interaction with the ventral striatum. *Neuroscience*, 30: 77–86.

Caine, S.B., Heinrichs, S.C., Coffin, V.L. and Koob, G.F. (1995) Effects of the dopamine D–1 antagonist SCH-23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. *Brain Res.*, 692: 47–56.

Calabresi, P., Maj, R., Pisani, A., Mercuri, N.B. and Bernardi, G. (1992) Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J. Neurosci.*, 12: 4224–4233.

Carlsen, J. and Heimer, L. (1986) The basolateral amygdaloid complex as a cortical-like structure. *Brain Res.*, 441: 377–380.

Chevalier, G. and Deniau, J.M. (1990) Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci.*, 13: 277–280.

Colwill, R.M. and Rescorla, R.A. (1988) Associations between the discriminative stimulus and the reinforcer in instrumental learning.- *J. Exp. Psychol. Anim. Behav. Process.*, 14: 155–164.

Cools, A.R. (1980) Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: facilitation of processes involved in selecting the best strategy in a stressful situation. *Behav. Brain Res.*, 1: 361–78.

Cools, A.R., van den Bos, R., Ploeger, G. and Ellenbroek, B.A. (1991) Gating function of noradrenaline in the ventral striatum: its role in behavioural responses to environmental and pharmacological challenges. In: P. Willner and J. Scheel-Krüger (Eds), *The Mesolimbic Dopamine System: from Motivation to Action*, Chichester, John Wiley and Sons, pp. 139–171.

Cousins, M.S., Sokolowski, J.D. and Salamone, J.D. (1993) Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. *Pharm. Biochem. Behav.*, 46: 943–951.

Davis, M. (1992) The role of the amygdala in conditioned fear. In: J.P. Aggleton (Ed.), *The Amygdala*, New York, Wiley-Liss Inc., pp. 255–306.

Davis, M., Walker, D.L. and Lee, Y. (1997) Amygdala and bed nucleus of the stria terminalis: differential roles in fear and anxiety measured with the acoustic startle reflex. *Philos. Trans. R. Soc. (Lond.) B.*, 352: 1675–1687.

Deniau, J.M., Kitai, S.T., Donoghue, J.P. and Grofova, I. (1982) Neuronal interactions in the substantia nigra pars reticulata through axon collaterals of the projection neurons: an electrophysiological and morphological study. *Exp. Brain Res.*, 47: 105–113.

Di Ciano, P., Blaha, C.D. and Phillips, A.G. (1998) Conditioned changes in dopamine oxidation currents in the nucleus accumbens of rats by stimuli paired with self-administration or yoked-administration of *d*-amphetamine. *Eur. J. Neurosci.*, 10: 1121–1127.

Dickinson, A. (1980) *Contemporary Animal Learning Theory*. Cambridge: Cambridge University Press.

Dickinson, A. (1985) Actions and habits – the development of behavioral autonomy. *Philos. Trans. R. Soc. (Lond.) B.*, 308: 67–78.

Dickinson, A. and Balleine, B. (1994) Motivational control of goal-directed action. *Anim. Learn. Behav.*, 22: 1–18.

Dickinson, A., Balleine, B., Watt, A., Gonzalez, F. and Boakes, R.A. (1995) Motivational control after extended instrumental training. *Anim. Learn. Behav.*, 23: 197–206.

Dickinson, A. and Dawson, G.R. (1987) Pavlovian processes in the motivational control of instrumental performance. *Q. J. Exp. Psychol. B*, 39: 201–213.

Divac, I. (1972) Neostriatum and functions of prefrontal cortex. *Acta Neurobiol. Exp.*, 32: 461–477.

Divac, I., Rosvold, H.E. and Szwarcbart, M.K. (1967) Behavioral effects of selective ablation of the caudate nucleus. *J. Comp. Physiol. Psychol.*, 63: 184–190.

Dunnett, S.B. and Iversen, S.D. (1980) Regulatory impairments following selective kainic acid lesions of the neostriatum. *Behav. Brain Res.*, 1: 497–506.

Dunnett, S.B. and Iversen, S.D. (1981) Learning impairments following selective kainic acid-induced lesions within the neostriatum of rats. *Behav. Brain Res.*, 2: 189–209.

Dunnett, S.B. and Iversen, S.D. (1982) Neurotoxic lesions of ventrolateral but not anteromedial neostriatum in rats impair differential reinforcement of low rates (DRL) performance. *Behav. Brain Res.*, 6: 213–226.

Evenden, J.L. and Carli, M. (1985) The effects of 6-hydroxydopamine lesions of the nucleus accumbens and caudate nucleus of rats on feeding in a novel environment. *Behav. Brain Res.*, 15: 63–70.

Everitt, B.J. (1990) Sexual motivation – a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats. *Neurosci. Biobehav. Rev.*, 14: 217–232.

Everitt, B.J., Cador, M. and Robbins, T.W. (1989) Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement. *Neuroscience*, 30: 63–75.

Everitt, B.J., Cardinal, R.N., Hall, J., Parkinson, J.A. and Robbins, T.W. Differential involvement of amygdala subsystems in appetitive conditioning and drug addiction. In: J.P. Aggleton (Ed.), *The Amygdala: A Functional Analysis*, Oxford, Oxford University Press, (in press).

Everitt, B.J., Fray, P., Kostarczyk, E., Taylor, S. and Stacey, P. (1987) Studies of instrumental behavior with sexual reinforcement in male rats (Rattus norvegicus). 1. Control by brief visual stimuli paired with a receptive female. *J. Comp. Psychol.*, 101: 395–406.

Everitt, B.J., Morris, K.A., O'Brien, A. and Robbins, T.W. (1991) The basolateral amygdala ventral striatal system and conditioned place preference: Further evidence of limbic striatal interactions underlying reward-related processes. *Neuroscience*, 42: 1–18.

Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P. and Robbins T.W. (1999) Associative processes in addiction and reward: the role of amygdala-ventral striatal subsystems. *Ann. NY Acad. Sci.*, 877: 412–438.

Everitt, B.J. and Robbins, T.W. (1992) Amygdala-ventral striatal interactions and reward-related processes. In: J.P. Aggleton (Ed.), *The Amygdala*, New York, Wiley-Liss.

Everitt, B.J. and Stacey, P. (1987) Studies of instrumental behavior with sexual reinforcement in male rats (Rattus norvegicus). 2. Effects of preoptic area lesions, castration, and testosterone. *J. Comp. Psychol.*, 101: 407–419.

Fisk, G.D. and Wyss, J.M. (1997) Pressor and depressor sites are intermingled in the cingulate cortex of the rat. *Brain Res.*, 754: 204–212

Floresco, S.B., Yang, C.R., Phillips, A.G. and Blaha, C.D. (1998) Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anaesthetized rat. *Eur. J. Neurosci.*, 10: 1241–1251.

Fredrikson, M., Wik, G., Fischer, H. and Andersson, J. (1995) Affective and attentive neural networks in humans: a PET study of Pavlovian conditioning. *NeuroReport*, 7: 97–101.

Freeman, J.H., Cuppernell, C., Flannery, K. and Gabriel, M. (1996) Limbic thalamic, cingulate cortical and hippocampal neuronal correlates of discriminative approach learning in rabbits. *Behav. Brain Res.*, 80: 123–136.

Gabriel, M. (1990) Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits. *Prog. Brain Res.*, 85: 467–483.

Gabriel, M., Kubota, Y., Sparenborg, S., Straube, K. and Vogt, B.A. (1991a) Effects of cingulate cortical lesions on avoidance learning and training-induced unit activity in rabbits. *Exp. Brain Res.*, 86: 585–600.

Gabriel, M. and Orona, E. (1982) Parallel and serial processes of the prefrontal and cingulate cortical systems during behavioral learning. *Brain Res. Bull.*, 8: 781–785.

Gabriel, M., Vogt, B.A., Kubota, Y., Poremba, A. and Kang, E. (1991b) Training-stage related neuronal plasticity in limbic thalamus and cingulate cortex during learning – a possible key to mnemonic retrieval. *Behav. Brain Res.*, 46: 175–185.

Gallagher, M. and Chiba, A.A. (1996) The amygdala and emotion. *Curr. Opin. Neurobiol.*, 6: 221–227.

Gallagher, M., Graham, P.W. and Holland, P.C. (1990) The amygdala central nucleus and appetitive Pavlovian conditioning: lesions impair one class of conditioned behavior. *J. Neurosci.*, 10: 1906–1911.

Gewirtz, J.C. and Davis M. (1997) Second-order fear conditioning prevented by blocking NMDA receptors in amygdala. *Nature*, 388: 471–474.

Goodale, M.A. and Milner, A.D. (1992) Separate visual pathways for perception and action. *Trends Neurosci.*, 15: 20–25.

Grace, A.A. (1987) An electrophysiologist's eye view of the basal ganglia. *Behav. Brain Sci.*, 10: 214–215.

Groenewegen, H.J., Berendse, H.W., Wolters, J.G. and Lohman A.H.M. (1990) The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala – evidence for a parallel organization. *Prog. Brain Res.*, 85: 95–118.

Haber, S.N. and McFarland, N.R. (1999) The concept of the ventral striatum in non-human primates. *Ann. NY Acad. Sci.*, 877: 33–48.

Hall, J., Parkinson, J.A., Connor, T.M.F., Di Ciano, P., Dickinson, A. and Everitt B.J. (1999) The role of amygdala-ventral striatal sub-systems in Pavlovian to instrumental transfer. *Soc. Neurosci. Abstr.*, 25: 90.

Han, J.S., Holland, P.C. and Gallagher, M. (1999) Disconnection of the amygdala central nucleus and substantia innominata/nucleus basalis disrupts increments in conditioned stimulus processing in rats. *Behav. Neurosci.*, 113: 143–151.

Han, J.S., McMahan, R.W., Holland, P. and Gallagher, M. (1997) The role of an amygdalo-nigrostriatal pathway in associative learning. *J. Neurosci.*, 17: 3913–3919.

Hatfield, T., Han, J.S., Conley, M., Gallagher, M. and Holland, P. (1996) Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *J. Neurosci.*, 16: 5256–5265.

Hearst, E. and Jenkins, H.M. (1974) *Sign tracking: the stimulus-reinforcer relation and directed action.* Austin, Texas: The Psychonomic Society.

Heimer, L., Alheid, G.F., deOlmos, J.S., Groenewegen, H.J., Haber, S.N., Harlan, R.E. and Zahm, D.S. (1997) The accumbens: beyond the core-shell dichotomy. *J. Neuropsychiatry Clin. Neurosci.*, 9: 354–381.

Hill, R.T. (1970) Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: E. Costa and S. Garratini (Eds), *Amphetamines and Related Compounds*, New York, Raven Press, pp. 781–795.

Hitchcock, J. and Davis, M. (1986) Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. *Behav. Neurosci.*, 100: 11.

Houk, J.C., Adams, J.L. and Barto, A.G. (1995) A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: J.C. Houk, J.L. Davis and D.G. Beiser (Eds.), *Models of Information Processing in the Basal Ganglia*, Cambridge, Massachusetts, London, MIT Press.

Houk, J.C. and Wise, S.P. (1995) Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. *Cereb. Cort.*, 2: 95–110.

Hurd, Y.L., McGregor, A. and Ponten, M. (1997) In vivo amygdala dopamine levels modulate cocaine self-administration behaviour in the rat: D1 dopamine receptor involvement. *Eur. J. Neurosci.*, 9: 2541–2548.

Hyde, T.S. (1976) The effect of Pavlovian stimuli on the acquisition of a new response. *Learn. Motiv.* 7: 223–239.

Jaspers, R., Schwarz, M., Sontag, K.H. and Cools, A.R. (1984) Caudate nucleus and programming behaviour in cats: role of dopamine in switching motor patterns. *Behav. Brain. Res.*, 14: 17–28.

Kelley, A.E., SmithRoe, S.L. and Holahan, M.R. (1997) Response-reinforcement learning is dependent on *N*-methyl-D-aspartate receptor activation in the nucleus accumbens core. *Proc. Natl Acad. Sci. USA*, 94: 12174–12179.

Kelley, A.E. and Stinus, L. (1985) Disappearance of hoarding behavior after 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with l-dopa. *Behav. Neurosci.*, 99: 531–545.

Kemp, J.M. and Powell, T.P.S. (1971) Connections of the striatum and globus pallidus: synthesis and speculation. *Philos. Trans. R. Soc. (Lond.), B* 262: 441–457.

Killcross, S., Robbins, T.W. and Everitt, B.J. (1997) Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. *Nature*, 388: 377–380.

Kim, J.J., Rison, R.A. and Fanselow, M.S. (1993) Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. *Behav. Neurosci.*, 107: 1093–1098.

Konorski, J. (1967) *Integrative Activity of the Brain.* Chicago: Chicago University Press.

Konorski, J. and Miller, S. (1937) On two types of conditioned reflex. *J. Genet. Psychol.*, 16: 264–272.

Koob, G.F., Riley, S.J., Smith, S.C. and Robbins, T.W. (1978) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. *J. Comp. Physiol. Psychol.*, 92: 917–927.

Lagowska, J. and Fonberg, E. (1975) Salivary reactions in dogs with dorsomedial amygdalar lesions. *Acta Neurobiol. Exp.*, 35: 17–26.

Louilot, A., Simon, H., Taghzouti, K. and Lemoal, M. (1985) Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala – a study by in vivo differential pulse voltammetry. *Brain Res.*, 346: 141–145.

Lovibond, P.F. (1983) Facilitation of instrumental behavior by a Pavlovian appetitive conditioned stimulus. *J. Exp. Psychol. Anim. Behav. Process.*, 9: 225–247.

Lyon, M. and Robbins, T.W. (1975) The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In: W.B. Essman and L. Valzelli (Eds), *Current Developments in Psychopharmacology*, Spectrum Publications Inc., N.Y., pp. 79–163.

Mackintosh, N.J. (1974) *The Psychology of Animal Learning.* London: Academic Press.

Maren, S., Aharonov, G. and Fanselow, M.S. (1997) Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav. Brain Res.*, 88: 261–274.

McAlonan, G.M., Robbins, T.W. and Everitt, B.J. (1993) Effects of medial dorsal thalamic and ventral pallidal lesions on the acquisition of a conditioned place preference – further evidence for the involvement of the ventral striatopallidal system in reward-related processes. *Neuroscience,* 52: 605–620.

McCullough, L.D., Cousins, M.S. and Salamone, J.D. (1993) The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: a neurochemical and behavioral study. *Pharmacol. Biochem. Behav.*, 46: 581–586.

Mirenowicz, J. and Schultz, W. (1996) Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. *Nature,* 379: 449–451.

Mishkin, M., Malamut, B. and Bachevalier, J. (1984) Memories and habits: two neural systems. In: G. Lynch, J.L. McGaugh and N.M. Weinberger (Eds), *Neurobiology of Learning and Memory*, New York, Guildford Press.

Mittleman, G., Brener, J. and Robbins, T.W. (1990) Physiological correlates of schedule-induced activities in rats. *Am. J. Physiol.*, 259: R485-R491.

Mogenson, G.J., Jones, D.L. and Yim, C.Y. (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog. Neurobiol.*, 14: 69–97.

Montague, P.R., Dayan, P. and Sejnowski, T.J. (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *J. Neurosci.,* 16: 1936–1947.

Moser, E., Moser, M.B. and Andersen, P. (1993) Spatial-learning impairment parallels the magnitude of dorsal hippocampal-lesions, but is hardly present following ventral lesions. *J. Neurosci.,* 13: 3916–3925.

Muir, J.L., Everitt, B.J. and Robbins, T.W. (1996) The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cereb. Cort.*, 6: 470–481.

Neafsey, E.J., Terreberry, K.M., Hurley, K.M., Ruit, K.G. and Frysztak, R.J. (1993) Anterior cingulate cortex in rodents: connections, visceral control functions, and implications for emotion. In: B.A. Vogt and M. Gabriel (Eds), *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comparative Handbook*, Boston, Birkhauser, pp. 206–233.

O'Brien, C.P., Ehrman, R.N. and Ternes, J.W. (1986) Classical conditioning in human opioid dependence. In: S.R. Goldberg and I.P. Stolerman (Eds.), *Behavioural Analysis of Drug Dependence*, London, Academic Press, pp. 329–356.

O'Donnell, P., Greene, J., Pabello, N., Lewis, B.L. and Grace, A.A. (1999) Modulation of cell firing in the nucleus accumbens. In: J. McGinty (Ed.), *Advancing from the Ventral Striatum to the Extended Amygdala, Ann. NY Acad. Sci.*, 887: 157–175.

Packard, M.G., Hirsh, R. and White, N.M. (1989) Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. *J. Neurosci.*, 9: 1465–1472.

Packard, M.G. and McGaugh, J.L. (1996) Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol. Learn. Mem.*, 65: 65–72.

Packard, M.G. and White, N.M. (1991) Dissociation of hippocampus and caudate nucleus memory systems by post-training intracerebral injection of dopamine agonists. *Behav. Neurosci.*, 105: 295–306.

Parkinson, J.A., Olmstead, M.C., Burns, L.H., Robbins, T.W. and Everitt, B.J. (1999a) Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive Pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by *d*-amphetamine. *J. Neurosci.*, 19: 2401–2411.

Parkinson, J.A., Robbins, T.W. and Everitt, B.J. (1999b) Selective excitotoxic lesions of the nucleus accumbens core and shell differentially affect aversive Pavlovian conditioning to discrete and contextual cues. *Psychobiology*, 27: 256–266.

Parkinson, J.A., Robbins, T.W. and Everitt, B.J. (2000a) Specific role for the central but not basolateral amygdala in appetitive emotional learning. *Eur. J. Neurosci.*, 12: 405–413.

Parkinson, J.A., Willoughby, P.J., Robbins, T.W. and Everitt, B.J. (2000b) Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: further evidence for limbic corticoventral striatopallidal systems. *Behav. Neurosci.*, 114: 42–63.

Pennartz, C.M.A. (1995) The ascending neuromodulatory systems in learning by reinforcement: comparing computational conjectures with experimental findings. *Brain Res. Rev.*, 21: 219–245.

Pennartz, C.M.A. and Kitai, S.T. (1991) Hippocampal inputs to identified neurons in an in vitro slice preparation of the rat nucleus accumbens – evidence for feedforward inhibition. *J. Neurosci.*, 11: 2838–2847.

Pennartz, C.M.A., Ameerun, R.F., Groenewegen, H.J. and Lopes da Silva, F.H. (1993) Synaptic plasticity in an in vitro slice preparation of the rat nucleus accumbens. *Eur. J. Neurosci.*, 5: 107–117.

Phillips, A.G., Pfaus, J.G. and Blaha, C.D. (1991) Dopamine and motivated behavior: Insights Provided by In Vivo Analyses. In: P. Willner and J. Scheel-Krüger (Eds), *The Mesolimbic Dopamine System: From Motivation to Action*, John Wiley and Sons, Chichester, pp. 199–224.

Phillips, R.G and LeDoux, J.E. (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.*, 106: 274–285.

Powell, D.A., Watson, K. and Maxwell, B. (1994) Involvement of subdivisions of the medial prefrontal cortex in learned cardiac adjustments in rabbits. *Behav. Neurosci.*, 108: 294–307.

Reading, P.J. and Dunnett, S.B. (1991) The effects of excitotoxic lesions of the nucleus accumbens on a matching to position task. *Behav. Brain Res.*, 46: 17–29.

Reading, P.J., Dunnett, S.B. and Robbins, T.W. (1991) Dissociable roles of the ventral, medial and lateral striatum on the acquisition and performance of a complex visual stimulus-response habit. *Behav. Brain Res.*, 45: 147–161.

Redgrave, P., Prescott, T.J. and Gurney, K. (1999a) The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience*, 89: 1009–1023.

Redgrave, P., Prescott, T.J. and Gurney, K. (1999b) Is the short-latency dopamine response too short to signal reward error? *Trends Neurosci.*, 22: 146–151.

Rescorla, R.A. and Solomon, R.L. (1967) Two-process learning theory: relationships between Pavlovian conditioning and instrumental learning. *Psychol. Rev.*, 74: 151–182.

Robbins, T.W. (1978) The acquisition of responding with conditioned reinforcement: effect of pipradol, methylphenidate, *d*-amphetamine and nomifensine. *Psychopharmacology*, 58: 79–87.

Robbins, T.W. and Everitt, B.J. (1992) Functions of dopamine in the dorsal and ventral striatum. *Semin. Neurosci.*, 4: 119–127.

Robbins, T.W., Giardini, V., Jones, G.H., Reading, P. and Sahakian, B.J. (1990) Effects of dopamine depletion from the caudate-putamen and nucleus accumbens septi on the acquisition and performance of a conditional discrimination task. *Behav. Brain Res.*, 38: 243–261.

Robbins, T.W. and Koob, G.F. (1980) Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. *Nature*, 285: 409–412.

Robbins, T.W., Rogers, R.D., Baunez, C. and Everitt, B.J. (1997) Lesions of medial and lateral striatum in the rat produce dissociable deficits in attentional performance. *Soc. Neurosci. Abstr.*, 23: 1838.

Robinson, T.E. and Berridge, K.C. (1993) The neural basis of drug craving – an incentive-sensitization theory of addiction. *Brain Res. Rev.*, 18: 247–291.

Robledo, P., Robbins, T.W. and Everitt, B.J. (1996) Effects of excitotoxic lesions of the central amygdaloid nucleus on the potentiation of reward-related stimuli by intra-accumbens amphetamine. *Behav. Neurosci.*, 110: 981–990.

Roozendaal, B., Oldenburger, W.P., Strubbe, J.H., Koolhaas, J.M. and Bohus B. (1990) The central amygdala is involved in the conditioned but not in the meal–induced cephalic insulin response in the rat. *Neurosci. Lett.*, 116: 210–215.

Rosvold, H.E. (1972) The frontal lobe system: cortical-subcortical interrelationships. *Acta Neurobiol. Exp.*, 32: 439–460.

Salamone, J.D. (1994) The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav. Brain Res.*, 61: 117–133.

Salamone, J.D., Kurth, P.A., McCullough, L.D., Sokolowski, J.D. and Cousins M.S. (1993) The role of brain dopamine in response initiation: effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. *Brain Res.*, 628: 218–226.

Salamone, J.D., Steinpreis, R.E., McCullough, L.D., Smith, P., Grebel, D. and Mahan K. (1991) Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. *Psychopharmacology*, 104: 515–521.

Schultz, W. (1994). Behavior-related activity of primate dopamine neurons. *Rev. Neurol. (Paris)*, 150: 634–639.

Schultz, W., Apicella, P., Romo, R. and Scarnati, E. (1995) Context-dependent activity in primate striatum reflecting past and future behavioral events. In: J.C. Houk, J.L. Davis and D.G. Beiser (Eds), *Models of Information Processing in the Basal Ganglia*, Cambridge, Massachusetts / London, MIT Press.

Schultz, W., Dayan, P. and Montague, P.R. (1997). A neural substrate of prediction and reward. *Science*, 275: 1593–1599.

Selden, N.R.W., Everitt, B.J., Jarrard, L.E. and Robbins, T.W. (1991) Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. *Neuroscience*, 42: 335–350.

Setlow, B. and McGaugh, J.L. (1998) Sulpiride infused into the nucleus accumbens post-training impairs memory of spatial water maze training. *Behav. Neurosci.*, 112: 603–610.

Setlow, B. and McGaugh, J.L. (1999) Differential effects of immediate post-training sulpiride microinfusions into the nucleus accumbens shell and core on Morris water maze retention. *Psychobiology*, 27: 248–255.

Sidman, M. and Fletcher, F.G. (1968) A demonstration of auto-shaping with monkeys. *J. Exp. Anal. Behav.*, 11: 307–309.

Simon, H., Taghzouti, K., Gozlan, H., Studler, J.M., Louilot, A., Herve, D., Glowinski, J., Tassin, J.P. and Le Moal, M. (1988) Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to d-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. *Brain Res.*, 447: 335–340.

Smith, J.W. and Dickinson, A. (1998) The dopamine antagonist, pimozide, abolishes Pavlovian-instrumental transfer. *J. Psychopharm.*, 12: A6.

Sokolowski, J.D. and Salamone, J.D. (1998) The role of accumbens dopamine in lever pressing and response allocation: effects of 6-OHDA injected into core and dorsomedial shell. *Pharmacol. Biochem. Behav.*, 59: 557–566.

Squire, L.R. (1986) Mechanisms of Memory. *Science*, 232: 1612–1619.

Stern, C.E. and Passingham, R.E. (1995) The nucleus accumbens in monkeys (Macaca-Fascicularis). 3. Reversal learning. *Exp. Brain Res.*, 106: 239–247.

Taylor, J.R. and Robbins, T.W. (1984) Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. *Psychopharmacology*, 84: 405–412.

Taylor, J.R. and Robbins, T.W. (1986) 6-hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with reward-related stimuli produced by intra-accumbens *d*-amphetamine. *Psychopharmacology*, 90: 390–397.

Terrace, H.S. (1981) Introduction: autoshaping and two-factor learning theory. In: C.M. Locurto, H.S. Terrace and J. Gibbon (Eds), *Autoshaping and Conditioning Theory*, New York, Academic Press.

Turken, A.U. and Swick, D. (1999) Response selection in the human anterior cingulate cortex. *Nature Neurosci.*, 2: 920–924.

Viaud, M.D. and White, N.M. (1989) Dissociation of visual and olfactory conditioning in the neostriatum of rats. *Behav. Brain Res.*, 32: 31–42.

Wagner, A.R. and Brandon, S.E. (1989) Evolution of a structured connectionist model of Pavlovian conditioning (AESOP). In: S.B. Klein and R.R. Mowrer (Eds), *Contemporary Learning Theories: Pavlovian conditioning and the status of traditional learning theory*, Hillsdale, NJ, Erlbaum.

Weiskrantz, L. (1956) Behavioural changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.*, 49: 381–391.

Whishaw, I.Q. and Kornelsen, R.A. (1993) Two types of motivation revealed by ibotenic acid nucleus accumbens lesions: dissociation of food carrying and hoarding and the role of primary and incentive motivation. *Behav. Brain Res.*, 55: 283–295.

Whitelaw, R.B., Markou, A., Robbins, T.W. and Everitt, B.J. (1996) Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behavior under a second-order schedule of reinforcement. *Psychopharmacology*, 127: 213–224.

Wickens, J. and Kötter, R. (1995) Cellular models of reinforcement. In: J.C. Houk, J.L. Davis and D.G. Beiser (Eds), *Models of Information Processing in the Basal Ganglia*, Cambridge, Massachusetts / London, MIT Press.

Wickens, J.R., Begg, A.J. and Arbuthnott, G.W. (1996) Dopamine reverses the depression of rat cortico-striatal

synapses which normally follows high-frequency stimulation of cortex in vitro. *Neuroscience*, 70: 1–5.

Wilcove, W.G. and Miller, J.C. (1974) CS-UCS presentations and a lever: human autoshaping. *J. Exp. Psychol.*, 103: 868–877.

Wilkinson, L.S., Humby, T., Killcross, A.S., Torres, E.M., Everitt, B.J. and Robbins, T.W. (1998) Dissociations in dopamine release in medial prefrontal cortex and ventral striatum during the acquisition and extinction of classical aversive conditioning in the rat. *Eur. J. Neurosci.*, 10: 1019–1026.

Williams, D.R. and Williams, H. (1969) Auto-maintenance in the pigeon: sustained pecking despite contingent non-reinforcement. *J. Exp. Anal. Behav.*, 12: 511–520.

Wilson, C.J. (1995) The contribution of cortical neurons to the firing pattern of striatal spiny neurons. In: J.C. Houk, J.L. Davis and D.G. Beiser (Eds), *Models of Information Processing in the Basal Ganglia*, Cambridge, Massachusetts/ London, MIT Press.

Wise, S.P. (1996) The role of the basal ganglia in procedural memory. *Seminars in the Neurosciences*, 8: 39–46.

Wolterink, G., Phillips, G., Cador, M., Donselaar-Wolterink, I., Robbins, T.W. and Everitt, B.J. (1993) Relative roles of ventral striatal D1 and D2 dopamine receptors in responding with conditioned reinforcement. *Psychopharmacology*, 110: 355–364.

Zaborszky, L., Alheid, G.F., Beinfeld, M.C., Eiden, L.E., Heimer, L. and Palkovits, M. (1985) Cholecystokinin innervation of the ventral striatum – a morphological and radioimmunological study. *Neuroscience*, 14: 427.

Zahm, D.S. and Brog, J.S. (1992) On the significance of subterritories in the accumbens part of the rat ventral striatum. *Neuroscience*, 50: 751–767.

Zahm, D.S., Jensen, S.L., Williams, E.S. and Martin, J.R. (1999) Direct comparison of projections from the central amygdaloid region and nucleus accumbens shell. *Eur. J. Neurosci.*, 11: 1119–1126.

Zeiler, M.D. (1972) Superstitious behavior in children: an experimental analysis. *Adv. Child Dev. Behav.*, 7: 1–29.

Zoli, M., Torri, C., Ferrari, R., Jansson, A., Zini, I., Fuxe, K. and Agnati, L.F. (1998) The emergence of the volume transmission concept. *Brain Res. Rev.*, 26: 136–147.