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The contribution of the amygdala, nucleus accumbens, and prefrontal cortex to emotion and motivated behaviour

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Abstract

Emotion and motivation depend on the assessment of the value of environmental stimuli. Multiple representations of stimulus value are created in the brain by Pavlovian and instrumental conditioning procedures. The basolateral amygdala (BLA) appears necessary for a Pavlovian conditioned stimulus (CS) to gain access to the current value of the specific unconditioned stimulus (US) that it predicts, while the central nucleus of the amygdala (CeA) controls brainstem arousal and response systems and subserves some forms of stimulus–response Pavlovian conditioning. The nucleus accumbens (Acb) appears not to be required to represent instrumental action–outcome contingencies, but influences instrumental behaviour strongly by mediating the impact of Pavlovian CSs on instrumental responding, and is required for the normal ability of animals to choose delayed rewards. Prelimbic cortex is required for action–outcome contingency detection, while insular cortex may allow rats to remember the sensory properties of foodstuffs and thereby retrieve their specific values. The orbitofrontal cortex (OFC) may represent aspects of reinforcer value governing instrumental choice behaviour. Finally, the anterior cingulate cortex (ACC) may play a role in responding to the emotional significance of stimuli and preventing responding to inappropriate conditioned stimuli.
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1. Introduction

Emotions and motivation both depend on our ability to assign value to events, objects, and states of the world. Such values drive our lives—thus, we seek out stimuli that are appetitive or rewarding and avoid those that are aversive. Though emotion and motivation are complex, the analysis of the neural basis of emotions has benefited from considering those brain systems that assign value to stimuli. Even within the rat there are many such systems, learning and representing different kinds of information about the world, as associative learning (including the acquisition of emotional value by a stimulus, context or event) is not a simple or unitary phenomenon. Overt behaviour is determined by the interaction of many learning and memory systems, some complementary, some competitive. In this review, the psychological and neural representations that govern two major classes of behaviour, Pavlovian and instrumental conditioned responding, will be summarized. Within this framework, the contributions to emotional and motivated behaviour of the amygdala, ventral striatum, and prefrontal cortex will be considered, in each case relating neural systems to the psychological representations to which they may correspond.

The term 'Pavlovian conditioning' (or classical conditioning) refers to a set of experimental procedures in which an experimenter arranges a contingency between stimuli in the world by presenting those stimuli independent of an animal's behaviour [1]. In a Pavlovian conditioning study, an initially neutral stimulus (such as a bell) is paired with a biologically relevant, unconditioned stimulus (US) (such as food) that normally elicits a reflexive or unconditioned response (UR) such as salivation. As a result of such pairings, the bell becomes a conditioned stimulus (CS), now capable of evoking salivation as a conditioned response (CR). Pavlovian conditioning (CS–US pairings) creates multiple associative representations in the brain [2–6]. Firstly, and most simply, the CS may become directly associated with the *unconditioned response* (UR), a stimulus–response association that carries no information about the identity of the US (e.g. Ref. [7]). However, a single US may elicit several responses; for example, a US such as a puff of air delivered to the eye may elicit a simple motor act such as blinking, and a 'central' process such as an enhancement of arousal or attention. Therefore, the CS may enter into stimulus–response associations with several kinds of response. Secondly, the CS can evoke a representation of *affect*—such as fear or the expectation of reward [8]. This embodies the concept of an emotional 'tone' that is tagged to a stimulus. Thirdly, the CS can become associated with the *specific sensory properties* of the US [4,9,10]—including its visual appearance, sound, feel, and smell, but also 'consummatory' qualities such as its taste and nutritive value.

Multiple representations are also found following instrumental conditioning, in which the experimenter arranges a contingency between the animal's behaviour and a reinforcing outcome [11]. It is apparent that at least six psychological processes contribute to learning and performance of instrumental behaviour [6,12,13]. Just as humans can be aware of the goals they seek, rats can conceptualize goals and actions symbolically and such representations can be in the form of declarative or semantic knowledge. Thus, goal-directed action in the rat depends on the twin representations of the *instrumental contingency* between an action and a particular outcome, and a representation of the outcome as a goal—termed the (instrumental) *incentive value* of the goal [13,14]. Simply put, a goal-directed organism presses a lever for food because it knows (1) that lever-

pressing produces food and (2) that it wants the food. What is not at all obvious intuitively is that this value, governing instrumental responding, differs from the 'hedonic' value that the rat experiences as it actually consumes the food. Though the instrumental incentive value normally tracks the 'hedonic' value closely, Dickinson and colleagues have shown in an elegant series of experiments that these values can be dissociated, being different from each other under certain circumstances [6,12,13]. A fourth factor governing instrumental performance is the presence of *discriminative stimuli* (S^Ds). When responding is rewarded in the presence of a stimulus but not in its absence, that stimulus is established as an S^D. S^Ds inform the subject that a particular instrumental (response–reinforcer) contingency is in force [15–17], though S^Ds also have properties of Pavlovian conditioned stimuli [18].

In addition to these sophisticated goal-directed systems, the rat can form *stimulus–response habits*, as long theorized [11,19–21]. S–R habits are the archetype of 'procedural' learning: as the S–R association is direct, there is no representation of the reinforcer. If a rat is responding via a goal-directed system for food, and that food is devalued (for example, by pairing it with lithium to induce nausea), the rat will subsequently respond less for that food. However, a rat responding using its habit system, which possesses no information about the reinforcer, will not alter its rate of responding following reinforcer devaluation. Habits appear to develop with extended training; thus, overtraining can cause instrumental responses to become 'habitual' and resistant to reinforcer devaluation [12,22–25].

Finally, Pavlovian CSs can modulate instrumental performance [12,13], an effect termed *Pavlovian–instrumental transfer* (PIT). For example, a stimulus that predicts the arrival of sucrose solution will enhance lever-pressing for sucrose [26,27]. PIT operates both by providing general conditioned motivation [28,29] and by selectively potentiating actions that share an outcome with the CS [18]. This Pavlovian motivational process is distinguishable from the values governing instrumental responding, psychologically (e.g. Ref. [30]) and pharmacologically [31]. PIT is functionally important as it probably plays a major role in CS-precipitated reinstatement of instrumental responding, exemplified by cue-induced relapse in drug addiction (see e.g. Refs. [32–34]).

Having summarized the psychological representations known to contribute to Pavlovian and instrumental behaviour in the rat, we will now review the contributions of the amygdala, nucleus accumbens, and prefrontal cortex to emotion and motivated behaviour, using the learning-theory framework outlined above.

2. Contributions of the amygdala to emotion and motivation

2.1. The amygdala comprises nuclei involved in emotional learning and expression

Since the demonstration that monkeys with amygdala lesions were 'fearless'—part of the Klüver–Bucy syndrome [35]—it has been recognized that the amygdala is a key part of the brain's emotional system. Damage to the amygdala in humans may lead to an increase in threshold of emotional perception and expression [36–38]; amygdala lesions cause impairments in emotional learning [39], deficits in the perception of emotions in

facial expressions [40,41], and impaired memory for emotional events (see Ref. [42]). The amygdala comprises several groups of nuclei [43–48]; two functional units that have been particularly implicated in the control of emotional processes are the central nucleus (CeA) and the basolateral amygdala (BLA). The BLA has extensive reciprocal projections with polysensory neocortex and the frontal lobes, and projects heavily to the ventral striatum and the CeA. In some situations, the BLA is responsible for important aspects of emotional Pavlovian learning; receiving sensory information via the lateral amygdala, it acts as a site of CS–US association and uses this learned information to control the activity of the CeA [49–57]. In turn, the CeA acts as a 'controller of the brainstem', using its widespread projections to the hypothalamus, midbrain reticular formation and brainstem to orchestrate behavioural, autonomic, and neuroendocrine responses. The BLA also projects to structures such as the ventral striatum and prefrontal cortex, enabling it to influence complex behaviour [58–60]. Additionally, the CeA itself receives direct sensory input [47,48,61,62] and is capable of learning and/or subserving behavioural expression, independently of the BLA [60,63–66]. How do these amygdaloid nuclei together contribute to motivated behaviour?

2.2. Amygdaloid subnuclei operate in series and in parallel

The amygdala is involved in Pavlovian conditioning of 'emotional' responses. Two measures frequently taken to indicate emotional states of fear in rats are freezing, a species-specific response to danger in which a rat remains motionless, and fear-potentiated startle, in which the presence of a stimulus signalling danger enhances the startle reflex to a loud noise. Lesions of either the BLA or CeA impair aversive conditioning indexed by these two measures [55,57]. The sensory thalamus, sensory neocortex, and hippocampus probably convey increasingly complex information about environmental stimuli (CSs) to the BLA, where CS–US association takes place [56]. Lesions of these structures, and lesions of targets of the CeA, such as the periaqueductal grey (PAG), lead to impairments in conditioned freezing [50,55–57]. A simple hypothesis incorporating these data is that the BLA acts as the associative site for stimulus–outcome representations and the CeA provides the output pathway through which these associations gain access to appropriate responses, such as the conditioned freezing response.

However, certain forms of fear conditioning may survive BLA lesions—specifically, contextual fear conditioning (as assessed by an aversion to the environment in which the subjects experienced shock) [67]. Furthermore, the CeA's contribution to aversive and appetitive associative learning does not depend solely on input from the BLA. For example, when rats are trained to respond on two levers for food, one of which intermittently produced a CS followed by mild electric shock, they exhibit two phenomena: instrumental avoidance (biasing their responding away from the lever producing the CS and shock) and Pavlovian conditioned suppression (inhibition of lever-pressing during presentation of the CS). While BLA lesions impair instrumental avoidance in this task, they do not affect conditioned suppression; in contrast, lesions of the CeA produce the opposite effect—preserved active avoidance and persistently impaired conditioned suppression [64]. An analogous double dissociation using an appetitive version of the task has also been reported [68]. Double dissociations of BLA and CeA function also exist within

the domain of appetitive conditioning: second-order conditioning requires the BLA but not the CeA, while conditioned orienting requires the CeA but not the BLA [63]; similarly, injections of dopamine antagonists into the CeA and BLA affect Pavlovian conditioned approach and instrumental responding for an appetitive conditioned reinforcer, respectively [65]. These data suggest that the BLA and CeA process information in parallel: representations stored in (or communicated through) the CeA and BLA can affect behaviour through separate afferent and efferent pathways. It is not surprising, then, that the CeA receives sensory input from the thalamus [61,62] and cortex [47], which could support association formation independent of the BLA (see also Ref. [69]), and that the BLA and CeA have dissociable and complementary efferent projections.

2.3. The basolateral amygdala (BLA) is required for a Pavlovian CS to gain access to the current motivational or affective value of the specific US that it predicts

Rats with BLA lesions are able to acquire conditioned responses [63,64,66–68,70]. However, these responses do not have the flexibility seen in intact animals. Specifically, they are insensitive to subsequent changes in the value of the US (reinforcer revaluation). For example, rats with BLA lesions have been shown to acquire normal conditioned responding to a CS paired with food [63]. BLA-lesioned rats also showed normal acquisition of an aversion to that food when it was subsequently paired with LiCl (Refs. [70,63], though see Ref. [71]), but failed to adjust their responding to the CS spontaneously after the food was devalued [63]. Similar results have been observed in monkeys [72]. The most parsimonious explanation is that the conditioned responses learned by the BLA-lesioned rats were a result of direct associations between the CS and the response. They lacked the ability to use the CS to access the value of a specific US and use that representation to alter their response (see also Ref. [73]).

This concept explains a number of other phenomena seen in BLA-lesioned animals. In second-order conditioning, a stimulus CS_1 is paired with a US, and a second stimulus CS_2 is then paired with CS_1. A second-order CS becomes associated with the affective value that is called up by the first-order CS, rather than its sensory properties [2,5]. Similarly, conditioned reinforcement depends on the affective or motivational value gained or accessed by the CS. BLA-lesioned rats cannot acquire second-order conditioning [63], cannot acquire responding under second-order instrumental schedules [74,75], and cannot use a first-order CS as a conditioned reinforcer [76,77]. BLA lesions also impair reward devaluation effects following first-order conditioning [63]—another task that requires the subject to retrieve the affective value of the US using the CS. Specific modulation of instrumental choice behaviour by a CS also requires that the subject utilizes the motivational value of a particular US; this capability, too, depends upon the BLA [64,68,78]. This hypothesis can also offer explanations as to why conditioned freezing and fear-potentiated startle are impaired by BLA lesions [6].

Thus, it seems likely that the BLA is necessary for a CS to retrieve the value of its specific US; once retrieved, this value may be used to control multiple responses (such as freezing, fear-potentiated startle, and instrumental choice behaviour) via different output systems. Very recent evidence suggests that the BLA is specifically involved in changing

the value retrieved by a CS: if a CS is paired with food before the BLA is destroyed, rats can use the acquired value of the CS to support new learning, but they cannot extinguish that value normally [194,195]. However, questions remain about the BLA's exact representational role [6] and the relationship between these psychological functions and the BLA's other prominent role in memory modulation (reviewed thoroughly by Refs. [42,79]).

2.4. The central nucleus of the amygdala (CeA) is a controller of brainstem arousal and response systems, and subserves some forms of stimulus–response Pavlovian conditioning

The CeA is a controller of the hypothalamus, midbrain and brainstem [69]; it projects to a variety of autonomic and skeletomotor control centres involved in aversive conditioned responding [50]. The CeA also projects, directly or indirectly, to reticular formation nuclei that provide the chemically defined, diffuse projections systems to the forebrain, such as the dopaminergic (DAergic) ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), the noradrenergic locus coeruleus, the serotonergic raphé nuclei, and basal forebrain cholinergic nuclei. As might be expected, a number of conditioned responses are dependent upon the CeA and its projection to this array of nuclei [60]. How does the role of the CeA differ from that of the BLA?

A number of Pavlovian conditioning tasks require the BLA but not the CeA. Thus, while producing deficits in a number of tests of Pavlovian conditioning, lesions of the CeA (unlike those of the BLA) do not impair second-order conditioning [63], or responding for conditioned reinforcement [80]. CeA-lesioned rats can acquire some first-order appetitive conditioned responses, such as conditioned behaviours directed at a food source [63,81]. Those first-order CRs that they do acquire are sensitive to reinforcer devaluation [63], implying that in CeA-lesioned rats a CS can still gain access to information about the identity and current value of its associated US.

Several specific Pavlovian conditioned responses require the CeA, but also the BLA. While CeA lesions abolish conditioned freezing, fear-potentiated startle and conditioned bradycardia [50–52,54,69,82–85], these behaviours are also sensitive to BLA lesions (as discussed above, and see Ref. [86]) and appear to depend on the CeA simply because the BLA gains access to these motor nuclei (PAG, PnC, dorsal motor nucleus of the vagus) via the CeA—part of its role in a serial circuit [56,69].

Some conditioned responses, however, depend on the CeA but not on the BLA. One such aversively motivated conditioned response is conditioned suppression, described earlier [6,64]. An appetitive example is conditioned locomotor approach (autoshaping), another CR that depends on the CeA but not the BLA [66]. Similarly, the rat's orienting response (OR) can be conditioned to a CS for food; conditioned ORs depend on the CeA (but not the BLA) [63,81]. Despite the lack of the conditioned response, the corresponding unconditioned response remains unimpaired in CeA-lesioned rats [81]. In fact, it has recently been found that CeA-lesioned rats exhibit deficits in conditioned orienting whether that response is engendered by Pavlovian conditioning procedures or explicit instrumental conditioning of the same response, though the lesion did not affect the rats' ability to detect instrumental contingencies when responses other than conditioned orienting were reinforced, and did not affect unconditioned orienting [87].

The role of the CeA also extends to Pavlovian conditioned motivational influences on instrumental action. Thus, PIT is abolished by lesions of the CeA, but not the BLA [64,68,88]; similarly, lesions of the CeA (but not the BLA) impair the ability of dopaminergic agonists to enhance responding for conditioned reinforcement [77,80].

Additionally, Gallagher, Holland and co-workers have shown that the CeA is involved in the control of attentional aspects of stimulus processing, through its projections to the reticular formation. The CeA plays a role in visuospatial attention during continuous-performance tasks [89], and also appears to regulate the *associability* of stimuli under certain circumstances [90–94]—that is, the ability of CSs to enter into new associations.

How can these functions of the CeA be brought together conceptually? Even though it receives neuronal afferents appropriate to support them, there is no direct evidence to suggest that the CeA is itself a site of association; it might receive an already-associated input. However, it is clear that animals lacking a BLA can form some kinds of association, the conditioned expression of which is sensitive to CeA, but not BLA, lesions [64,66,88,93,95]. The simplest analysis at present seems to be that the CeA does form simple CS–UR ('sensorimotor') associations, which do not depend upon a specific US: that is, they are independent of the identity and current motivational value of the US and are also unable to support second-order conditioning. It may be that the responses subserved by CeA-dependent associations especially include the modulation of reflexes organized within the brainstem, including some that might conventionally be regarded as 'affective', including conditioned suppression, conditioned orienting, and Pavlovian–instrumental transfer [6,60]. These are all disrupted by CeA but not BLA lesions. Responses such as conditioned suppression may influence instrumental behaviour nonspecifically (i.e. influence the ongoing level of all instrumental responses), but are insufficient to modulate instrumental behaviours differentially (i.e. affect choice) [64]. Finally, just as the BLA has a role in memory modulation [79], the CeA also modulates the associability of representations stored elsewhere in the brain [90,93,94].

2.5. Summary

It appears likely that the BLA stores associations which allow the CS to retrieve the affective or motivational value of its particular US, a form of Pavlovian stimulus–outcome association. This information can be used to control the CeA and thereby its hypothalamic, midbrain and brainstem targets, giving rise to 'affective' responses such as freezing or fear-potentiated startle and modulation of arousal and attention. The BLA can also use this information to modulate instrumental actions, presumably via its projections to the ventral striatum or prefrontal cortex (discussed next). In addition to its role as a recipient of information from the BLA, the CeA also receives parallel input from cortical and subcortical structures; it receives or may encode direct stimulus–response (S–R) Pavlovian associations, thereby influencing specific conditioned responses organized in the hypothalamus, midbrain, and brainstem, as well as modulating arousal and attention through the diffuse projection systems of the reticular formation.

3. The nucleus accumbens

Motivational effects of emotionally significant stimuli are mediated in part by the ventral striatum, specifically the nucleus accumbens (Acb) [96]. While the Acb conforms broadly to the pattern of the cortico-striatal-pallido-thalamo-cortical 'loop' typical of the striatum [97,98], it is a recipient of information from a considerable array of limbic structures (including the amygdala, hippocampal formation, and regions of the prefrontal cortex) [97] that also projects to structures known to be involved in behavioural expression. Therefore, the Acb has been suggested to represent a 'limbic–motor interface' [99]. On histochemical and anatomical grounds, the nucleus accumbens may be divided into core (AcbC) and shell (AcbSh) compartments [100,101]; both receive an important dopamine (DA) projection from the midbrain. Here, we will consider the contribution of the Acb to the psychological processes that motivate action (outlined earlier), and the manner in which it may be influenced by the amygdala.

3.1. The nucleus accumbens (Acb) is not required for goal-directed instrumental behaviour

The available evidence suggests that the Acb is not required for goal-directed action; Acb-lesioned rats are sensitive to changes in instrumental contingency [102,103,190] or the value of the instrumental outcome [102,190]. Similarly, DA receptor antagonists do not affect the representation of reinforcer value that governs such goal-directed actions [31]. Insofar as the issue has been addressed experimentally, stimulus–response habits persist following Acb lesions or DA depletion [104,105]. However, it is clear that Acb lesions influence responding on simple schedules. A major reason for this appears to be that Acb lesions impair the normal ability of Pavlovian CSs to enhance instrumental responding (see Ref. [6]).

3.2. The Acb mediates the motivational impact of Pavlovian conditioned stimuli

Pavlovian mechanisms are routinely involved when motivated animals procure goals. When a CS has been associated with an appetitive outcome, such as food, the CS may elicit the conditioned response of locomotor approach to the CS (termed autoshaping) [106]. Autoshaping, in which appetitive CSs attract attention and elicit approach [107,108], often has the beneficial function of drawing an animal closer to sources of natural rewards. It may also play a detrimental role in attracting humans towards artificial reinforcers such as drugs of abuse, maintaining addiction and inducing relapse [109–111]. In addition, animals will subsequently work for the CS, a situation in which the CS acts as a conditioned reinforcer [2]. Conditioned reinforcement is a significant mechanism that enables animals to obtain long-term goals (see Ref. [112]). Finally, presentation of the CS can enhance ongoing instrumental responding [26,27], termed Pavlovian–instrumental transfer. PIT may be important in addiction (with potential roles in acquisition, maintenance, and cue-induced relapse; [32–34]) as it represents a mechanism by which uncontrolled (noncontingent) stimuli can radically affect goal-directed respond-

ing. All three phenomena—autoshaping, conditioned reinforcement, and PIT—involve the AcbC.

Excitotoxic lesions of the AcbC, but not the AcbSh, impair the acquisition of an autoshaped appetitive approach response in rats [113]. Furthermore, AcbC lesions impair the performance of the conditioned response in rats lesioned after the response was trained [114], just as they impair temporally discriminated Pavlovian approach to a single CS predictive of food [115]. Similarly, 6-OHDA-induced DA depletion of the Acb impairs both the acquisition and performance of autoshaping [116].

Neither the AcbC, the AcbSh, nor the DA innervation of the Acb is required for rats to acquire a new response with conditioned reinforcement [115,117]. However, it is clear that this DA innervation *enhances* the action of conditioned reinforcers. Thus, amphetamine greatly potentiates responding for conditioned reinforcement when injected directly into the Acb [118], an effect that is anatomically, behaviourally and pharmacologically specific [117–119]. It appears that information about the conditioned value of a CS depends upon the BLA and is conveyed to the Acb where its effects can be potentiated by DA [120].

The Acb is also critical for the behavioural impact of *noncontingent* Pavlovian conditioned stimuli, as demonstrated clearly by the phenomenon of PIT; 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 [26,27]. Noncontingent presentation of an appetitive CS elevates AcbC DA [121,122]. Lesions of the AcbC [88] abolish PIT (see also Refs. [123,190]), as does systemic treatment with DA receptor antagonists [31,124]. Similarly, PIT can be enhanced by intra-accumbens amphetamine in the same way that conditioned reinforcement is [125]. Finally, PIT is also impaired by CeA lesions [88,95]. It is therefore likely that the ability of an appetitive Pavlovian CS to potentiate instrumental behaviour depends on the mesolimbic DA system innervating the Acb, possibly under the control of the CeA [60,88,96].

3.3. The AcbC promotes responding for delayed rewards

It has recently been shown that the integrity of the Acb is also critical for animals to tolerate delays to reward. In a task in which rats were offered the choice of an immediate, small reward or a larger, delayed reward, selective lesions of the AcbC severely impaired rats' ability to choose the delayed reward; that is, AcbC-lesioned rats made impulsive choices [126,127]. The possibility that the AcbC is required to maintain the value of a reinforcer over a delay may provide a novel insight into Acb function, as it is not clear that these results are explicable in terms of a deficit in the expression of Pavlovian conditioning. These results also show that the Acb is involved in action selection even when those actions do not differ in response effort or cost; thus, reduced preference for delayed reinforcement may explain the observations that Acb DA depletion prevents rats working hard for a preferred food [128] and impairs responding on high-effort schedules [129], as such schedules also impose delays to reinforcement (though see Ref. [191]). It is not presently known which afferents convey specific information about the value of delayed reinforcers to the

AcbC, but as lesions of the anterior cingulate cortex (ACC) or medial prefrontal cortex (mPFC) had no effect on impulsive choice [126], obvious candidates are the BLA and orbitofrontal cortex [192], both implicated in the assessment of reward value and probability [59,130].

3.4. The nucleus accumbens shell (AcbSh) mediates the motivational impact of unconditioned stimuli

There is less behavioural evidence relating the AcbSh to specific learning processes. For example, lesions of the AcbSh leave aversive Pavlovian conditioning to both discrete and contextual cues intact [131], do not impair appetitive Pavlovian approach behaviour [113,115], and do not prevent rats responding for conditioned reinforcement [115]. However, extracellular DA release, particularly within the AcbSh, is sensitive to primary reinforcement. DA increases in the AcbSh have been reported in response to unconditioned stimuli such as food [121] and cocaine [122]. Unconditioned aversive stimuli also increase DA release in the Acb [132], specifically the AcbSh [133]. However, conditioned stimuli do not elevate AcbSh DA, elevating DA in the AcbC instead [121,122] (see also Ref. [134]).

In turn, the AcbSh influences a number of unlearned behaviours. The AcbSh appears to provide an influence on feeding through its interactions with the lateral hypothalamus [135]. For example, selective intra-AcbSh infusions of the AMPA receptor antagonist DNQX or the GABA(A) receptor agonist muscimol stimulate feeding [136–138]. This effect resembles that seen following electrical stimulation of the lateral hypothalamus; indeed, the feeding induced by DNQX infusion into the shall can be blocked by concurrent inactivation of the lateral hypothalamus [139]. It has been argued that the AcbSh provides a high-level control system able to switch between basic behavioural patterns based on primary motivational states; for example, to override feeding behaviour if a predator approaches [135]. Like the AcbC, the AcbSh also influences locomotor behaviour: dopaminergic stimulation of the AcbSh induces locomotion [140], while the locomotor stimulant effects of amphetamine depend on the AcbSh [115]. It is possible that while the AcbC mediates a conditioned influence on behaviour, the AcbSh may provide a qualitatively similar influence, but responding to unconditioned stimuli [6].

3.5. Summary

The nucleus accumbens has a role in modulating unconditioned behaviours such as feeding and locomotion, and learned behaviour (including instrumental responding). It is a key site mediating the ability of Pavlovian CSs to invigorate and direct behaviour, being critical for autoshaping (the influence of Pavlovian CSs on locomotion), the effect of dopaminergic systems to magnify the effect of conditioned reinforcers on instrumental responding, and PIT. This motivational influence of Pavlovian CSs has been termed *incentive salience* [141,142], or ‘Pavlovian incentive value’ [31], to distinguish it from the instrumental incentive value of Dickinson and Balleine [12,13]. Additionally, the Acb appears to support animals’ ability to work for delayed rewards; one possible explanation

is that the Acb provides motivation to choose a delayed reward that normally offsets the effects of the delay.

4. The prefrontal cortex and its interactions with the amygdala and nucleus accumbens

In the rat, the prefrontal cortex (PFC) is a heterogeneous region of the brain that includes the prelimbic, anterior cingulate, agranular insular and orbitofrontal areas [143,144]. Each of these regions makes a distinct contribution to emotional or motivated behaviour. This final section will review studies that have examined the contribution of the PFC to simple conditioning tasks, primarily in the rat, and will of necessity omit a great deal of research into complex functions of the PFC (such as working memory, attention and 'executive' control [145]).

4.1. Prelimbic cortex: instrumental contingency detection and extinction

In the rat, the contribution of the prelimbic cortex (part of the medial prefrontal cortex, mPFC) to motivated behaviour appears to involve the detection of instrumental (action–outcome) contingencies. It is possible to test this specifically. For example, rats may be trained to perform two actions concurrently for two different food rewards; in addition, one of those reinforcers may be delivered noncontingently with respect to the subjects' behaviour. The degree of action–outcome contingency for this reinforcer, P(outcome|action) − P(outcome|no action), is thus selectively degraded. Using this technique, it has been shown that although lesions of prelimbic cortex do not prevent rats acquiring instrumental performance, or, in separate tests, from discriminating between the two actions and the two reinforcers, such lesions render the rats insensitive to this contingency manipulation [146,193]. This suggests that such rats might truly be 'creatures of habit', learning to press levers via their stimulus–response habit system.

Goal-directed action requires that instrumental contingencies interact with the incentive value of goals, and as described earlier, the BLA may be involved in the neural representation of incentive value. Interestingly, the connection between the BLA and the mPFC has recently been shown to be involved in the ability of rats to modulate instrumental choice behaviour in response to conditioned punishment [147]; thus, the anatomical connection between the BLA and the mPFC [48] might represent a functional link between incentive value and instrumental contingencies.

Additionally, electrolytic lesions of the ventral mPFC, i.e. prelimbic/infralimbic cortex (but not dorsal mPFC or ventrolateral, agranular insular cortex) interfere with the extinction of Pavlovian conditioned freezing to a discrete CS in the rat [148–150]. Similarly, the prelimbic cortex in the mouse interacts with the amygdala and may function to suppress inappropriate conditioned freezing [151]. As extinction does not simply represent 'unlearning' but may involve the learning of new, inhibitory ('CS → not-US') associations [2], these findings may be related to the long-standing view that the PFC mediates behavioural inhibition [152–154], with different specific aspects of inhibition being mediated by different regions within the PFC [155,156]. Reconciling these

perspectives on prelimbic cortex function will require both experimental and theoretical developments.

4.2. Insular cortex: memory for specific sensory aspects of food, used to retrieve value information

Lesions of the insular cortex, the primary gustatory cortex in the rat [157], do not impair responding on the instrumental contingency test just described. However, such lesions appear to impair rats' ability to store or retrieve the memory of the incentive value of a food reward in the absence of that reward [146,158], perhaps because they cannot remember the *specific sensory* properties (tastes) of the instrumental outcomes [158].

The insular cortex may have a similar role in Pavlovian conditioning: mnemonic retrieval of specific sensory aspects of the food US may depend on gustatory neocortex [73]. Rats with gustatory neocortex lesions reduce their consumption of a flavour paired with LiCl, and show normal unconditioned orofacial rejection responses, but do not show conditioned orofacial responses [159]. Conditioned orofacial responses [160,161] may depend on the retrieval of specific sensory aspects of the US [162,163]. Thus, Holland [73] has suggested that insula-lesioned rats have access to the conditioned motivational value of the food (hence the rats drink less following conditioning), and perceive tastes normally, but cannot retrieve the taste of the food using a CS.

4.3. Orbitofrontal cortex and representations of reinforcer value

The orbitofrontal cortex (OFC) has been widely suggested to guide behaviour based on the anticipated value of different actions [164,165]; it is extensively and reciprocally connected to the BLA [166]. Humans with OFC damage are impaired on a number of tests of emotional reactivity to stimuli, and make poor decisions as a result [167]; in several respects, they resemble amygdala-lesioned subjects [168]. For example, in the laboratory 'gambling task' of Bechara et al. [167], subjects choose between decks of cards; some decks pay out small rewards steadily, with the occasional small loss, for a net gain, while other decks pay out much larger rewards but the occasional losses are catastrophic. Normal subjects learn to prefer the safe decks, and develop an autonomic response (including a skin conductance response, SCR) that precedes their choice and is especially pronounced when they are about to choose a 'risky' deck. OFC-lesioned patients do not develop anticipatory SCRs and consistently perform poorly on the task. Damasio [165] have suggested that these autonomic responses represent 'somatic markers', a rapidly retrieved ''utility signal'' that normally acts to speed up and improve decision-making by 'pre-biasing' other, computationally intensive cognitive systems, preventing them from considering particularly bad courses of action.

Such decision-making may represent instrumental choice behaviour based on the incentive value of the alternative outcomes. The OFC is a particularly strong candidate for a representation of incentive value, as its neurons respond rapidly to changes in the reward value of specific foods. For example, neurons in primate OFC respond to reward but discriminate between different rewards in doing so [169,170]. When a monkey is fed to satiety with a particular food, the OFC responses to its flavour or odour decline, while the

responses to other foods are unaffected [171], paralleling the behavioural change induced by sensory-specific satiety. Similarly, OFC lesions impair monkeys' ability to alter behaviour in response to changes in the emotional significance of stimuli [155,156]. Like the amygdala, the OFC is well placed to process specific value information, as it receives projections from polymodal sensory cortex [166] in addition to motivational state information from the hypothalamus. Recently, direct evidence for a functional connection between the BLA and OFC has been provided by Baxter et al. [172], who showed that disconnecting these two structures impaired the ability of rhesus monkeys to adjust their choice behaviour in response to reinforcer devaluation. These data are consistent with the notion that the OFC influences instrumental choice behaviour and interacts with value systems in the amygdala to do so, but the nature of this interaction is not yet clear.

4.4. Anterior cingulate cortex: stimulus specificity of conditioned responses?

The anterior cingulate cortex (ACC) is part of the midline PFC that has been strongly implicated in emotional processing. Although a rough equivalence may be drawn across the ACC of rodents, monkeys and humans [166,173], the focus of research on the primate ACC has so far differed from that on the rat. It is clear that the primate ACC, at least, is involved in a wide range of motivationally-oriented unconditioned behaviour [174]; the human ACC is implicated in mood disorders, in processing the emotional significance of stimuli, in attentional function, and in detecting errors of performance (see Ref. [6]). Here, we will concentrate on rodent ACC function.

The rodent ACC has been strongly implicated in appetitive and aversive stimulus–reinforcer learning. It receives nociceptive information and coordinates autonomic responses [173,175,176]; early studies found that aspirative ACC lesions attenuated classically conditioned bradycardia in the rabbit [177]. The rabbit ACC is also involved in active avoidance behaviour, a task combining aspects of Pavlovian and instrumental conditioning. When rabbits must learn to step in response to a tone CS+ in order to avoid a shock, while ignoring a different tone (CS−), Gabriel et al. have shown that discriminated neuronal activity (neuronal firing to the CS+ but not the CS−) develops early in avoidance training [178–181]. Lesions of the ACC impair acquisition of the avoidance response [182,183].

In the rat, the ACC has been more extensively studied using appetitive tasks, which also suggest that it has a role in stimulus–reinforcer association. For example, lesions of the ACC impair the acquisition of an eight-pair concurrent discrimination task, in which subjects must learn which stimulus in each of eight pairs of complex visual stimuli must be selected in order to obtain reward [184]. Furthermore, ACC lesions impair the acquisition of stimulus–reward associations in autoshaping [113,185]. Autoshaping depends not only on the ACC and the AcbC (discussed earlier) but on a functional connection between the two [113], while lesions of other afferents to the AcbC do not impair autoshaping [66,185,186]. Thus, the ACC appears to provide the critical glutamatergic projections to the AcbC for normal Pavlovian conditioned approach.

Although the data summarized above strongly implicate the ACC in stimulus–reinforcer association, recent findings suggest that Pavlovian conditioning can occur in the absence of the ACC and suggest that the ACC makes a highly specific contribution to

conditioning. In a recent study [187], we found that ACC-lesioned rats could learn simple conditioned approach tasks, despite being impaired at autoshaping; they could also utilize a Pavlovian CS as a conditioned reinforcer, and exhibited normal conditioned freezing and PIT. Thus, they performed normally in all tasks in which a single CS was used, but were impaired on tasks involving multiple CSs (including autoshaping and a two-stimulus approach task designed to establish the critical behavioural difference between autoshaping and the simpler, one-stimulus conditioned approach task at which they were unimpaired). It is noteworthy that multiple CSs have been used in a wide range of other tasks in which ACC lesions impair performance [113,182–185,188,189]. On the basis of these data from rodents, we have suggested [6,96,187] that the ACC 'disambiguates' similar CSs for its corticostriatal circuit on the basis of their differential association with reinforcement, preventing generalization between the CSs.

4.5. Summary

The PFC makes many contributions to motivated behaviour; its functions are starting to be related to basic processes of Pavlovian and instrumental conditioning. Analysis of the basic processes performed by the PFC will likely provide a foundation from which to understand its contribution to complex functions such as 'executive control'. Additionally, PFC subregions, particularly the OFC and ACC, make important contributions to representations of value and emotion. The prelimbic cortex, involved in working memory and attention, has also been implicated in action–outcome contingency detection, while the rodent insular cortex has a role in mnemonic retrieval of taste information (and through it, representations of incentive value). The OFC is a strong candidate for the representations of instrumental incentive value, and interacts heavily with the amygdala. The ACC has been directly implicated in human emotional disorders; it may respond to the emotional significance of stimuli but also to errors of performance, using this information to 'disambiguate' responding and prevent responding to inappropriate stimuli. Recent interventional studies in rodents are beginning to make links to correlational studies in humans (see Ref. [6]) with the aim of a better understanding of the mechanisms of motivation.

5. Conclusions

Emotion, motivation and reinforcement are not unitary. Pavlovian conditioning creates multiple representations whose neural bases are dissociable (see also Ref. [6]); these include CS–US (sensory) or S–S associations, dependent at least in part on the gustatory neocortex for food USs; CS–US (motivational) associations, suggested to depend on the BLA for both appetitive and aversive conditioning; direct CS–affect associations, which are poorly understood; and CS–response associations, whose neural basis depends on the specific response (being CeA-dependent in the case of several responses including conditioned suppression and PIT). The anterior cingulate cortex is also implicated in stimulus–reinforcement association and the attribution of emotional significance to stimuli; in the rodent, it may act to prevent other neural systems from generalizing between CSs erroneously.

Other structures contribute to instrumental conditioning, which also creates multiple representations and which can be heavily influenced by Pavlovian conditioning procedures. The prefrontal (prelimbic) cortex is critical for the perception of instrumental contingencies in rats, while gustatory neocortex also has a role in recalling the instrumental incentive values of foodstuffs. It is not yet known how either structure acquires or represents this information, or how each interacts with other representations of stimulus and reward value such as those in the amygdala and orbitofrontal cortex. It seems likely that the dorsal striatum contributes in some way to the acquisition of S–R responding (see Ref. [96]), but this requires definitive proof. The nucleus accumbens, originally described as a limbic–motor interface [99], is a Pavlovian–instrumental interface; in addition to promoting the efficacy of delayed rewards, it is a critical site for the motivational and directional impact of Pavlovian CSs on instrumental responding and on locomotor approach.

Humans are plagued by disorders of emotion (such as depression, anxiety, and phobias) and motivation (such as impulsivity and addiction). To understand and treat such disorders rationally, it is important that the underlying neural systems contributing to normal and abnormal behaviour are better understood. Such understanding may be aided by applying well-defined psychological concepts to the study of these neural systems.

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