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Review

Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates

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Abstract

The prefrontal cortex has been implicated in a variety of cognitive and executive processes, including working memory, decision-making, inhibitory response control, attentional set-shifting and the temporal integration of voluntary behaviour. This article reviews current progress in our understanding of the rodent prefrontal cortex, especially evidence for functional divergence of the anatomically distinct sub-regions of the rat prefrontal cortex. Recent findings suggest clear distinctions between the dorsal (precentral and anterior cingulate) and ventral (prelimbic, infralimbic and medial orbital) sub-divisions of the medial prefrontal cortex, and between the orbitofrontal cortex (ventral orbital, ventrolateral orbital, dorsal and ventral agranular cortices) and the adjacent medial wall of the prefrontal cortex. The dorso-medial prefrontal cortex is implicated in memory for motor responses, including response selection, and the temporal processing of information. Ventral regions of the medial prefrontal cortex are implicated in interrelated 'supervisory' attentional functions, including attention to stimulus features and task contingencies (or action–outcome rules), attentional set-shifting, and behavioural flexibility. The orbitofrontal cortex is implicated in lower-order discriminations, including reversal of stimulus–reward associations (reversal learning), and choice involving delayed reinforcement. It is anticipated that a greater understanding of the prefrontal cortex will come from using tasks that load specific cognitive and executive processes, in parallel with discovering new ways of manipulating the different sub-regions and neuromodulatory systems of the prefrontal cortex.

Keywords: Prefrontal cortex; Orbitofrontal cortex; Inhibitory control; Cognition; Visuo-spatial attention; Spatial working memory; Noradrenaline; Dopamine; Acetylcholine; Serotonin

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1. Introduction

The prefrontal cortex has been the focus of considerable scientific investigation in recent years, owing in part to the growing recognition that dysfunction of this region and associated circuitry probably underlies many of the cognitive and behavioural disturbances associated with major neuropsychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. Recent findings in rodents and non-human primates suggest that divergent cognitive processes may be carried out by anatomically distinct sub-regions of prefrontal cortex [3,16,17,26,27,38,39,72,100,101,118,124], although the extent to which these processes can be considered functionally homologous in different species remains controversial [13]. This article reviews evidence of functional localization in different sub-regions of the rat prefrontal cortex in cognition and executive control, especially within the context of our own empirical and theoretical analysis of prefrontal cortex functioning and rodent behaviour.

2. The rodent prefrontal cortex: structural organization

One major obstacle to cross-species research of the prefrontal cortex has been the long-standing debate over what constituents equivalent regions of prefrontal cortex between different species [13,60,96,105,123]. The main reason for this uncertainty lies in the fact that the prefrontal cortex as a whole shows enormous variation across species in terms of established anatomical criteria such as cytoarchitectonics and connectivity, especially the presence or absence of a granular zone and the existence of strong reciprocal connections from the mediodorsal nucleus of the thalamus [60,96,105,115,123]. Nevertheless, based on Rose and Woolsey's definition of prefrontal cortex as cortex in receipt of reciprocal connections from the mediodorsal thalamus [115], as well as other criteria [123], several distinct regions of prefrontal cortex can be identified in the rat (see Fig. 1). The first is a *medial* frontal division, which can be sub-divided into a dorsal region that includes precentral (PrC) and anterior cingulate (ACg) cortices and a ventral component that includes the prelimbic (PrL), infralimbic (IL) and medial orbital (MO) cortices. The second is a *lateral* region that includes the dorsal and ventral agranular insular (AID, AIV) and lateral orbital (LO) cortices. Finally, a *ventral* region can be delineated that encompasses the ventral orbital (VO) and ventral lateral orbital (VLO) cortices. Unlike posterior and temporal regions of neocortex, the prefrontal cortex (as well as premotor cortical areas), receive highly organized inputs from the basal ganglia via striatopallidal and striatonigral projections, and subsequently pallidothalamic and nigrothalamic projections that project, in a parallel segregated manner, to different areas of prefrontal cortex [60]. In addition to thalamocortical connections, the prefrontal cortex receives extensive cortico-cortical inputs, for example, from posterior parietal cortex and sensory cortical areas, as well as connections form subcortical structures such as the substantia nigra, ventral tegmental area, amygdala, lateral hypothalamus and hippocampus [60,76]. There are also reciprocal connections from the prefrontal cortex to these structures, as well as direct projections to the lateral septum, mesencephalon and autonomic regions of the brainstem [60,76]. The prefrontal cortex also targets, in a reciprocal and topographical manner, the main nuclei of origin of the major forebrain cholinergic and monoaminergic neurotransmitter systems,

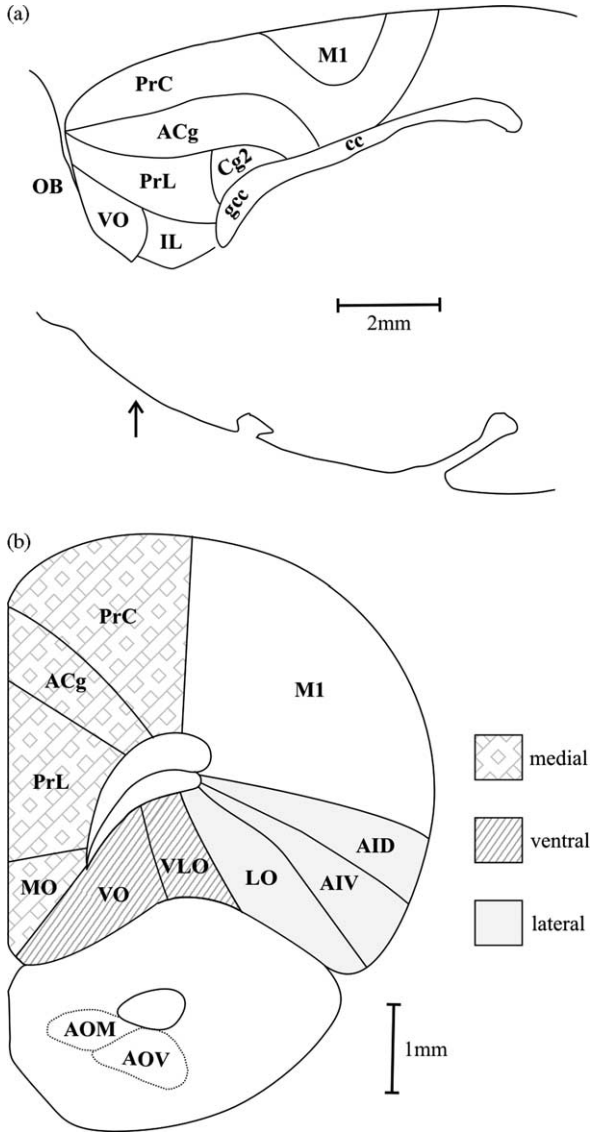

Fig. 1. Illustrative diagrams of the rat prefrontal cortex (adapted from [72,76,103,123]). (a) Lateral view, 0.9 mm from the midline. (b) Unilateral coronal section, approximately 3.5 mm forward of bregma (depicted by the arrow above). The different shadings represent the three major subdivisions of the prefrontal cortex (*medial*, *ventral* and *lateral*). Abbreviations: ACg, anterior cingulate cortex; AID, dorsal agranular insular cortex; AIV, ventral agranular insular cortex; AOM, medial anterior olfactory nucleus; AOV, ventral anterior olfactory nucleus; cc, corpus callosum; Cg2, cingulate cortex area 2; gcc, genu of corpus callosum; IL, infralimbic cortex; LO, lateral orbital cortex; M1, primary motor area; MO, medial orbital cortex; OB, olfactory bulb; PrL, prelimbic cortex; PrC, precentral cortex; VLO, ventrolateral orbital cortex; VO, ventral orbital cortex.

including noradrenaline (NA)-containing neurons in the pontine central grey, dopamine (DA) neurons in the ventral tegmental area, serotonin (5-HT) neurons in the raphé nuclei and acetylcholine (ACh) neurons in the basal forebrain [112]. These systems act in turn to *neuromodulate* cortical networks by influencing inhibitory and excitatory synaptic transmission as well as other cortical processes [6,63,112].

3. Functions of the rodent prefrontal cortex

Studies in rats, monkeys and humans accord with the view that the prefrontal cortex contributes to *executive functioning*, or in other words, that set of cognitive control processes that are necessary for optimal scheduling of complex sequences of behaviour, including attentional selection and resistance to interference, monitoring, behavioural inhibition, task switching, planning and decision-making [9,13,54,84,96,99,100,102,105,110,112]. A more general view holds that the prefrontal cortex is critical for the 'on-line' maintenance of memory representations, which is necessary for the mediation of contingencies of action over time, especially under conditions of interference [9,13,54,83,127]. A debate in recent years is whether the so-called executive components of working memory should be considered unitary or heterogeneous in nature, and whether they can be fractionated according to the different anatomical divisions of prefrontal cortex [9,110]. Research in rodents [26,27,72,100,118] and primates [38,39] is consistent with the notion of functional heterogeneity in the prefrontal cortex, although it is less clear how these apparently dissociable regions of prefrontal cortex are organized, for example, in a hierarchical manner or as independent functional units, and whether they differ primarily in informational content or the operational processes they perform [110].

4. Mnemonic processes

The prefrontal cortex has been strongly implicated in working memory processes ([5,14,15,34,52,58,70,79,94,106,118,121,130]; for review see [72]). Working memory is a temporary memory system composed of distinct, but overlapping cognitive processes used for the active maintenance and elaboration of task-relevant information. It can be defined operationally as memory that is required for one trial of an experiment, but not for subsequent trials. Studies linking the prefrontal cortex with working memory processes in rodents usually involve tasks with a *delayed* response contingency, including spatial delayed alternation [72,76,79,121,130] and delayed non-matching to sample [3,48,71,72,76]. Rats with lesions of the PrL and IL, but not ACg or orbitofrontal cortex, are profoundly impaired on such tasks when delays are imposed [34,72,76].

It is widely acknowledged that working memory processes are subject to modulatory influences, especially with respect to the prefrontal dopaminergic and cholinergic systems [5,14,15,48,52,106,130]. Intra-prefrontal administration of the D1 agonist SKF 81297 impairs delayed alternation performance [130], and either disrupts or facilitates memory retrieval on a delayed win-shift paradigm depending on the strength of the memory trace (with disruption at short delays and enhancement at long delays [52]). In addition, functional antagonism of D1 receptors

apparently facilitates delay-associated activity of pyramidal neurons in the prefrontal cortex [127], implying that working memory may depend in part, on an optimal level of D1 receptor 'tone' in the prefrontal cortex, possibly according to an inverted 'U-shaped' function [112]. This may be relevant to deficits in prefrontal cortex function reported in rats and monkeys during exposure to mild stress [6], and the proposal that increased levels of DA and NA (acting at α1 receptors) suppresses prefrontal cortical functioning, thus enabling faster, more instinctive behaviours to manifest [6,130].

The putative involvement of the cholinergic innervation of the prefrontal cortex in working memory has also been investigated [15,48,106]; however, there is some debate whether cholinergic manipulations primarily affect mnemonic processes. For example, infusions of the muscarinic ACh receptor antagonist scopolamine in the hippocampus produce dose- and delay-dependent impairments on delayed non-matching to position tasks, but the same compound infused into the medial prefrontal cortex produces dose-, but not delay-dependent deficits [48]. Broersen and colleagues [15] instead found that intra-prefrontal scopolamine induced both a dose- and delay-dependent impairment, whereas the deterioration of performance induced by D1 and D2 antagonists depended on dose but not delay. More recently, it has been reported that muscarinic cholinergic receptors in distinct sub-regions of the medial prefrontal cortex contribute differentially to spatial working memory [106]. Thus, scopolamine infusions in the PrL/IL cortices, but not ACg cortex, impaired spatial working memory in a dose- and delay-dependent manner [106], and this is consistent with previous demonstrations that ACg lesions do not generally affect working memory for spatial location [72].

However, attributing deficits on delayed response tasks solely in terms of working memory processes is often confounded by the dependency of such tasks on ancillary prefrontal cortex functions such as response selection, egocentric spatial processing, switching, set shifting and the curtailment of inappropriate motor behaviour [13,72,76,85]. Thus, some or all of the reported learning and memory impairments reported in rats on delayed response tasks may instead reflect disturbances in one or more of these component processes [13]. Indeed, based on a series of experiments involving reversible lidocaine-induced lesions of the ACg or PrL [118], the PrL appears not to be involved in the encoding of delayed spatial win-shift behaviour on an eight-arm radial maze (i.e. temporary lesions made before the encoding stage had no effect on later test performance), but instead, is involved in the later retrieval or use of this information. Lesions of the ACg (and PrC, in part) prior to the encoding stage did impair accurate performance during the test phase 30 min later, but temporary lesions made immediately after encoding did not disrupt later performance. The ACg lesions also disrupted random foraging behaviour, with subjects showing a perseverative tendency to re-visit previously baited arms. These findings indicate that neither the PrL nor the ACg are actively involved in the *storage* and maintenance of information across a time delay. Rather, these data are consistent with the notion that the prefrontal cortex contributes to the organization, planning and flexibility of behaviour, based on previously acquired information.

5. Temporal sequencing of behaviour

A prominent view of the prefrontal cortex is that it mediates contingencies of action over time, or in other words, the cross-temporal organization of behaviour [54,77]. Findings in rodents support this view. Rats with lesions of the medial prefrontal cortex are reliably impaired on tasks that require several behavioural responses to be carried out sequentially [76], and ACg lesions impair memory for the temporal order of spatial information [72]. In addition, aspirative lesions of the medial prefrontal cortex impair rats' ability to time extrinsic stimuli [47]. In a recent study, Delatour and Gisquet-Verrier [36] examined the role of the ACg in behavioural sequencing. Rats with lesions of the ACg were trained on two tasks, both of which involved response selection, but only one required behavioural sequencing. The first, a delayed conditional Go/No-Go discrimination task, required rats to press a lever following a light stimulus to earn food reward, or to withhold from responding following a tone stimulus. The task involved delayed responding, but not sequencing of motor responses. ACg-lesioned rats showed no deficits on this task. By contrast, they were impaired in acquiring a spatial delayed alternation task that involved sequencing different responses (left and right turns). It is possible that the ACg lesions affected egocentric memory [72], but is unlikely because deficits are also found on tasks where there are no explicit egocentric cues, such as the spatial win-shift task [118].

6. Attentional processes

Accumulating evidence supports a role for the prefrontal cortex in attentional functions [12,17,26,28,38,35,57,95]. In non-human primates, lesions of the dorsolateral prefrontal cortex, but not orbitofrontal cortex, produce deficits in shifting from one perceptual dimension to another (extra-dimensional attentional set shifting), whereas lesions of the orbitofrontal cortex, but not dorsolateral cortex, impair reversal learning [38,39]. Similar dissociations have been found in rodents with lesions of the medial and orbitofrontal cortices [12,13]. Thus, in rats trained to discriminate bowls containing food on the basis of odor, digging medium, or the texture covering the bowls, lesions of the medial prefrontal cortex (PrL, IL, and with partial damage to Cg1, Cg2 and anterior PrC) produce a selective deficit in extradimensional set-shifting [12]. Conversely, lesions of the orbitofrontal cortex (VLO/VO) impair reversal learning, but not the acquisition of intradimensional and extradimensional

set-shifting [13]. Recently, a role for the orbital prefrontal cortex in reversal learning (i.e. a reversal of the stimulus–reward *contingency*) has been confirmed using a touchscreen testing procedure for visual discrimination learning [26]. The perseverative nature of the deficits on this, and other visual discrimination tasks [17], implies that behaviour is less *flexible* in prefrontal cortex-lesioned animals. This has clear relevance for the widely held notion that the medial prefrontal cortex mediates shifts between new strategies or rules [13,33,71,72,107]. Specifically, rats with permanent or transient lesions of the medial prefrontal cortex (PrL/IL) are impaired in switching from spatial- to visual-cued versions of the Morris water maze [33] and cheese-board task [107], as well as switching from a non-match-to-sample to a match-to-sample rule [71]. It has been proposed that reversal learning represents a relatively low-order rule, that is, a rule based on object valence with no change in perceptual processing [72,129]. By contrast, higher order rules represent more abstract relationships between different features of the environment, especially the classification of information according to a particular dimension [72,129]. Thus, the PrL and IL may be involved in the selection of higher order rules (e.g. cross-modal attentional shifts), whereas the orbitofrontal cortex may be involved in lower order rules (reversal learning) [72,107,129]. This is compatible with the hypothesis that the *medial* prefrontal cortex acts to preserve attentional selectivity to relevant stimulus features during learning [17].

6.1. The 5-choice serial reaction time task

One paradigm that has been widely used to assess attentional and executive functions in rodents is the 5-choice serial reaction time task (5-CSRTT) [25,27,30,57,78,80,82,100,109,113]. The 5-CSRTT, which is analogous to the human continuous performance tests of sustained attention [113], requires subjects to scan a horizontal array of five spatial apertures for the location of a brief visual target stimulus over a large number of discrete trials (see Fig. 2). At its core, the task taxes attentional capacity, as indexed by the *accuracy* of reporting of stimuli, in addition to inhibitory response control or executive functioning. Accuracy is measured by the ratio of correct responses to the total number of correct and incorrect responses. Incorrect responses, or errors of commission, refer to responses made in an aperture where the target stimulus had not been presented. Variations in accuracy cannot be accounted for by non-specific influences such as motivational factors or perturbed motor behaviour because correct and incorrect responses require the same motor effort [113]. At least two types of inhibitory response control can be indexed on the 5-CSRTT; firstly *premature responses*, which occur during the inter-trial interval (ITI) before the target stimulus has been presented and are generally interpreted as a form of impulsive behaviour [25,26,31,62], and secondly, *perseverative responses*, in which rats continue to respond at the apertures after the presentation of the target, akin to a form of compulsive over-responding [113]. Premature responses relate to a disturbance in *preparatory* response mechanisms, whereas perseveration reflects a failure to disengage from responding once initiated. A number of other behavioural variables are normally also measured on the 5-CSRTT, including errors of omissions (which may reflect inattentiveness [109]), latency to respond correctly, and reward collection latency, the latter an index of motivation [113]. Since correct responses are sometimes made in the presence

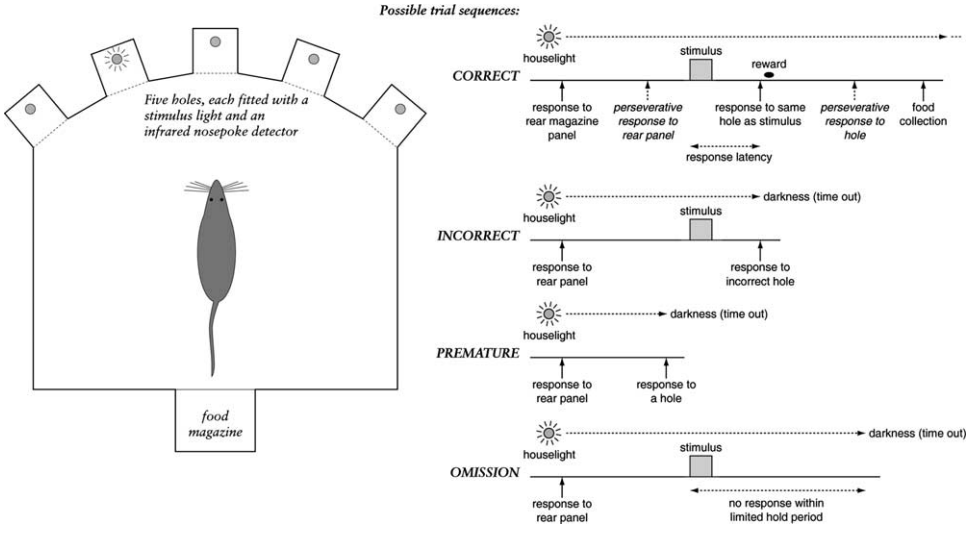

Fig. 2. The five-choice serial reaction time task (5-CSRTT). Left: apparatus, consisting of a chamber with a rear magazine equipped with a pellet dispenser and a mechanism for detecting head entries (nosepokes) into that magazine (adapted from [25]). At the front of the chamber is an array of five equally spaced holes, each equipped with a light bulb and an infrared nosepoke detector. Right: possible trial sequences in the task. Subjects initiate trials by responding to the rear magazine; after a delay, a brief stimulus is presented in one of the five holes. Subjects must respond to that hole (*correct response*) within a certain time to win food. If they respond to the wrong hole (*incorrect response*), respond before the stimulus is presented (*premature response*), or fail to respond (*omission*), they are punished with a period of darkness before the next trial begins.

of the stimulus, or as is more typical, within approximately 0.25 s of its offset, decision processes in this task are evidently quite rapid under baseline conditions. However, disturbances in response latency and choice are observed in rats with lesions of the medial prefrontal cortex [84,93,100], and this may reflect impaired decision-making [84,93].

Variations in attentional functioning and performance on the 5-CSRTT can be achieved by altering the duration, brightness and frequency of the target stimuli [25,28,32,93, 100,113]. For example, the timing of the stimuli can be altered on a trial-by-trial basis ('event onset asynchrony') to prevent subjects relying on self-pacing to anticipate the onset of the target stimulus. Conversely, selective attention can be indexed by presenting distracting bursts of white noise just prior to the onset of the visual target stimulus. Finally, in specific circumstances, presenting the stimuli with high frequency over many trials ('high event rate') can produce a so-called vigilance decrement, that is, a selective decline in attentional accuracy over the course of the session [31]. In this variant of the task, sustained attentional functioning is taxed because attentional resources need to be allocated on a continuous basis [113].

6.1.1. Lesion studies

Damage to relatively distinct regions of the rat prefrontal cortex with glutamatergic excitotoxins such as quinolinic acid impairs performance on the 5-CSRTT [27,28,93,100]. Lesions encompassing the ACg and PrL cortices result in a substantial and long-lasting impairment in choice accuracy (attentional selectivity) and a slower latency to respond correctly [93]. Rats with lesions of the *post*-genual ACg cortex exhibit a clear increase in impulsive (premature) responding post-operatively, but show no other impairments in attentional performance [93]. Recently, advances have been made with more focussed lesions of the different frontal sectors. Specifically, attentional selectivity appears to be particularly related to damage to the pregenual region of the ACg cortex [100], impulsive premature responding to IL cortex damage [27] and perseveration to orbitofrontal cortex damage [27]. However, although lesions of the PrL have no effect on attentional accuracy they do increase perseverative responding [28]. Thus, there is evidently some degree of functional overlap in the different sub-regions of prefrontal cortex, which may be related to the precise contingencies of the 5-CSRTT. For example, orbitofrontal lesions appear to increase perseverative responding when the inter-trial interval is *long* and *unpredictable* [27], whereas PrL lesions increase perseveration under baseline conditions (i.e. a fixed inter-trial interval), and possibly also when the stimulus duration is reduced [28]. This accords with evidence that lesions incorporating the ACg, PrL and IL cortices produce large increases in perseveration, but lesions of the ACg do not [100]. Thus, attentional selectivity in the visual domain appears to reside mainly in dorsomedial areas of prefrontal cortex (ACg), whereas ventral and lateral regions appear critical for inhibitory response control, possibly in a divergent, but complementary manner, according to the requirements imposed by different task contingencies. Studies with simple Pavlovian conditioning tasks suggest that one role for the peri-/postgenual ACg may be to discriminate similar stimuli on the basis of their differential association with reinforcement [18]; rats with such lesions exhibit Pavlovian conditioning, as assessed by a wide range of response systems, but are impaired at discriminating between a reinforced CS+ and a non-reinforced CS−.

6.1.2. Neuromodulatory influences

The ascending monoaminergic (NA, DA and 5-HT) and cholinergic (ACh) systems contribute to different aspects of performance on the 5-CSRTT [113]. Lesions of the cortically projecting cholinergic neurons of the nucleus basalis magnocellularis made using excitotoxins, or the highly selective cholinergic immunotoxin 192 IgG-saporin [64,126], generally impair discriminative performance [80, 82,92], especially during the increased attentional demand imposed by high event rates, shortened duration of the target stimuli, or the concurrent presentation of auditory distractors. Infusions of 192 IgG-saporin directly into the ventromedial PFC also impair performance on this task, specifically with a vigilance decrement under high event rate and increased impulsiveness and perseveration [31]. This is compatible with evidence that cholinergic afferents in the medial prefrontal cortex modulate neuronal activity associated with increased attentional demand [56], and the more general hypothesis that the cortical cholinergic system functions to optimize attentional resources within a system of limited processing capacity [122]. Destruction of the ascending noradrenergic projections to the frontal cortex by infusions of 6-hydroxydopamine into the dorsal noradenergic ascending bundle also impairs attentional accuracy, but only when the targets are presented unpredictably in time, during D-amphetamine challenge, or in the presence of white noise distraction [25,29,113]. Based on these findings, the ACh and NA systems appear to contribute to rather similar operational processes relevant to visual attention, presumably in a manner serving to maintain discriminative selectivity in the face of interference. In well-trained animals, however, established performance on the 5-CSRTT is associated with large increases in PrL ACh release, but not NA release [30,83,98], suggesting that the two systems, though functionally distinct, probably act in a complementary manner to facilitate attentional processing. Less is known of the role of the prefrontal DA systems in the 5-CSRTT, but depletion of NA and DA from the medial prefrontal cortex results in attentional impairments, specifically during a variable short ITI contingency [113]. The effects on performance of global 5-HT depletion, produced by infusions of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into the dorsal raphé nucleus (which mainly innervates the neocortex and striatum) are characterized by

a long-lasting *increase* in premature or impulsive responding and a transient improvement in accuracy [62].

Further clues to the modulatory functions of the cortical monoaminergic and cholinergic systems have accrued from the direct intra-prefrontal administration of dopaminergic and serotonergic compounds during performance on the 5-CSRTT [57,78,100,128]. Improvements in attentional performance are found after local administration of a D1 receptor agonist into ACg/PrL [57], whereas SCH 23390 (a D1 receptor antagonist) impairs attentional selectivity and sulpiride (a D2 antagonist) has no effect. Functional antagonism of 5-HT2a receptors in the prefrontal cortex with ketanserin [100] or M100907 [128] reduces impulsive premature responding, in addition to improving discriminative accuracy [128]. Facilitated attentional performance also results after local administration of the 5-HT1a agonist 8-OH-DPAT [128], but ACg infusions of the 5-HT2a/2c agonist DOI [(2,5-dimethoxy-4-iodophenyl)-2-aminopropane] have no effect on attention or impulsivity [78]. An important principle emerging from these studies is that 5-HT1a and 5-HT2a receptors interact in a functionally opposing manner to regulate component behavioural processes on the 5-CSRTT. Similar interactions probably also occur with respect to 5-HT2a and 5-HT2c receptors [113], which may explain the lack of effects of DOI on performance. Additional studies with selective 5-HT2a and 5-HT2c agonists may resolve this issue.

6.1.3. Functional neurochemistry

The 'on-line' measurement of ACh, DA, NA and 5-HT release in the prefrontal cortex during behavioural testing on the 5-CSRTT, as well as other attentional paradigms, has been a major catalyst in fuelling hypotheses on the functions of the neuromodulatory systems originating in the reticular core of the brain [30,31,32,66,82,98]. This approach offers a powerful way of inferring function, especially if it can be shown that different task requirements (or contingencies) affect one neurotransmitter system and not another. It is now known, for example, that performance on visual attentional paradigms, including the 5-CSRTT, leads to large and sustained increases in cortical ACh release [30,66,82,98], consistent with a purported involvement of the basal forebrain cortical cholinergic system in visual attentional processes [82,92,113,122]. In contrast, task performance has much less of an impact on prefrontal NA levels under baseline conditions [30], but on a one-choice variant of the paradigm, the release of PrL DA (as well as its metabolite DOPAC) increased substantially following task onset [31]. The fact that DOPAC also increases on the 5-CSRTT, despite no change in NA efflux [30], implies that the 5-CSRTT engages the prefrontal DA system, in addition to the cholinergic system. The cortical 5-HT system is unaffected by continuous performance on a one-choice variant of the 5-CSRTT [31], although individual 5-HT levels in the PrL correlate positively with impulsive behaviour [31]. This is consistent with the intracerebral infusion studies reviewed above, as well as recent findings that isolation-reared rats are less impulsive on the 5-CSRTT, in addition to having *reduced* extracellular levels of 5-HT in the PrL [32].

Our working hypothesis is that the neuromodulatory systems of the prefrontal cortex are functionally specialized, and that each are engaged by different feedback circuits appropriate to the level of processing required. What is required now is a clearer understanding of the different cognitive control processes that ACh, DA, NA and 5-HT modulate, and whether signalling is distributed, or localized within the different sectors of the prefrontal cortex.

7. Action–outcome associations and the rodent prefrontal cortex

7.1. Goal-directed actions and habits; action–outcome contingency

When animals learn to perform actions for rewarding outcomes, they do so via several psychological mechanisms (see [19,40,41,43]). One important such mechanism is 'goal-directed' action, corresponding directly to the human concept of intentional acts. Thus, when a rat presses a lever to obtain food, it may do so for several reasons, but one is that it has learned the *contingency* between its action and the outcome; desiring the outcome, therefore, it performs the action to obtain its goal. This may be contrasted to 'habitual' (stimulus–response, S–R) responding, in which stimuli become directly connected to (associated with) motor responses—by this mechanism, a rat might press a lever 'unthinkingly' because the environmental stimuli evoke the response directly, as a consequence of the rat's history of receiving reinforcement following lever-pressing. Goal-directed actions are more flexible than habits. For example, if the experimenter causes the rat no longer to desire the food in question (outcome devaluation, perhaps induced by poisoning the food, or by feeding it to the rat to the point of satiety), the goal-directed agent will adjust its behaviour immediately, ceasing to respond now that the food is no longer a goal. In contrast, the habitual agent cannot alter its behaviour without further experience. Despite their relative inflexibility, habits may confer advantage on the agent that possesses them. It has long been theorized that performance of a habit requires fewer cognitive resources than goal-directed action [69]; the formation of a habit may 'free up' cognitive resources for other tasks. With extended training, actions that were originally goal-directed can become 'automatized' and habitual [1,41,42,44,45], consistent with this theory.

The ability to perceive action–outcome (A–O) contingencies depends on more than detecting whether or not an action is reliably followed by the outcome. This factor could be written $P(O|A)$, the probability that an outcome occurs given that the animal has performed the action.

Contingency, however, depends also on $P(O|\neg A)$, the probability that an outcome occurs given that the animal has *not* performed the action Fig. 3a–e) [42,61]. Specifically, contingency can be measured as $P(O|A)$–$P(O|\neg A)$. For example, an action might be followed by reward with perfect reliability, $P(O|A)=1$, and yet there might be no contingency between the action and the outcome if $P(O|\neg A)=1$ as well—if the reward arrives 'for free' whether or not the subject presses the lever, there is no action–outcome contingency. Contingency detection, therefore, requires the animal to represent the difference between the 'background' rate of reinforcement and the rate of reinforcement following its action.

Finally, factors other than contingency affect instrumental learning. Animals are also sensitive to action–outcome *contiguity*, the temporal proximity between action and outcome. Even if the action–outcome contingency is perfect, delays between the action and the outcome profoundly impair learning [46,59,80], perhaps because it can be hard to discriminate between a situation in which outcomes are delivered as a consequence of the animal's action, but after a delay, and a situation in which outcomes are delivered fairly frequently, but independently of their behaviour [41].

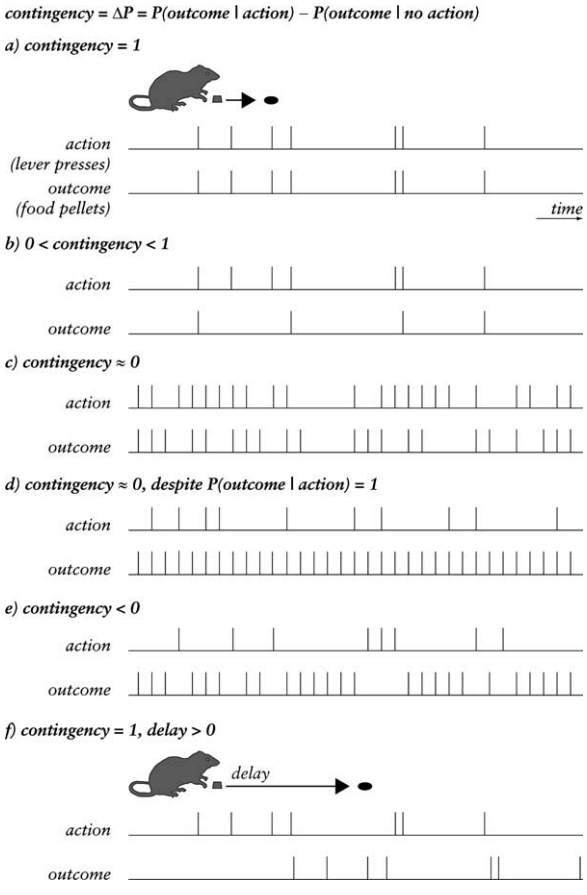

Fig. 3. Action–outcome contingency. The contingency may be stated as P(outcome|action)–P(outcome|no action), where $P(A|B)$ denotes 'the probability that A occurs, given that B has occurred'. A variety of contingencies are illustrated, from 1 (perfect positive contingency) through 0 (no relationship between the action and the outcome) to −1 (perfect negative contingency; the action prevents the outcome). Row (d) illustrates that the contingency can be zero even if the outcome occurs whenever the action is performed; this situation occurs when the 'background' rate of outcome delivery is sufficiently high. Row (f) illustrates another problem that animals must sometimes face when evaluating action–outcome contingencies: even if the contingency is perfect, action–outcome delays may make the contingency harder to detect.

7.2. The prelimbic cortex and action–outcome contingency detection

In the rat, the prelimbic cortex (PrL) is required for the detection of instrumental (action–outcome) contingencies [10]. It is important to note that to demonstrate that a structure is necessary for detection of action–outcome contingencies requires more than showing that an animal cannot acquire instrumental responding in its absence. Indeed, were one to prevent an animal from perceiving contingencies, there is every reason to think that instrumental performance *would* be acquired, via a habit system. Explicit tests of contingency perception are thus required. For example, rats may be trained to perform two actions concurrently for two different food rewards. Subsequently, one of those reinforcers may be delivered non-contingently with respect to the subjects' behaviour, as well as contingently; in other words, 'free' reinforcer is given, increasing $P(O|\neg A)$. The degree of action–outcome contingency for this reinforcer, $P(O|A)$–$P(O|\neg A)$, is thus selectively degraded. Although lesions of PrL do not prevent rats from acquiring instrumental performance, or, in separate tests, from discriminating between the two actions and the two reinforcers, they render the rats insensitive to this contingency manipulation [10]. Furthermore, rats with PrL lesions do not work less for foods that have been devalued by prefeeding than they work for valued foods [10,75]. This suggests that instrumental conditioning in rats with damage to the PrL is based solely on S–R habit learning.

7.3. Medial prefrontal cortex and extinction

Additionally, electrolytic lesions of the ventral medial prefrontal cortex (mPFC), i.e. prelimbic/infralimbic cortex (but not dorsal mPFC or ventrolateral, agranular insular cortex) interfere with the extinction of a Pavlovian conditioned freezing response to a discrete CS in the rat [89–91], although they do not affect extinction in all preparations [53]. Similarly, the PrL in the mouse may interact with the amygdala to suppress inappropriate conditioned freezing [55]. As extinction does not simply represent 'unlearning', but may involve the learning of new, inhibitory ('CS→not-US') associations [80], these findings may be related to the long-standing view that the PFC mediates behavioural inhibition [68,85,110], with different

specific aspects of inhibition being mediated by different regions within the PFC [4,26,27,38,39].

7.4. Infralimbic cortex (IL) and habits

In contrast to the effects of PrL lesions, which appear to remove rats' capacity for goal-directed action and leave their actions driven by S–R habits, lesions of infralimbic cortex (IL) appear to have the opposite effect. In normal rats, extended training with an appropriate schedule of reinforcement can render actions habitual and insensitive to devaluation of the outcome, when once they were goal-directed and sensitive to outcome devaluation [1,41,42,44,45]. Lesions of IL appear to delay or prevent the acquisition of S–R habits, such that IL-lesioned rats remain goal-directed (sensitive to devaluation of the outcome) after prolonged training at a point where normal rats do not [75].

7.5. Prefrontal ACh, NA and action–outcome contingency shifts

Consistent with the previous discovery that the PrL is critical for contingency detection in rats [10], we have observed substantial neurochemical changes in the PrL in response to a direct manipulation of action–outcome contingency in the 5-CSRTT [30]. The manipulation is shown in Fig. 4: well-trained rats were assigned to pairs, with one rat from each pair being designated the master rat and the other the yoked control (slave). The master rat continued to perform the 5-CSRTT normally. The slave, however, experienced exactly the same stimuli (lights and food pellets) as the master, but its behaviour had no programmed consequences. Each master–slave pair, therefore, experienced the same environment, but not the same action–outcome contingencies. The loss of contingency produced a substantial and sustained decrease in ACh efflux in the PrL, together with a significant elevation in NA efflux [30]. These data imply that the prefrontal noradrenergic system, unlike the cortical cholinergic system, is engaged by *novel* action–outcome contingencies, compatible with a role in mechanisms of plasticity and new learning. One possibility is that noradrenergic inputs in the PrL, and possibly other regions of prefrontal cortex, provide an important means for re-directing attentional focus and selectivity in the face of heightened arousal [7,114]. This is consistent with the recently proposed state-dependent model of locus coeruleus function in which phasic and tonic changes in activity are hypothesized to promote focused and scanning attention, respectively [8], and with the observation that activation of central NA mechanisms can apparently lead to improvements in shifting of attention between different cues [37].

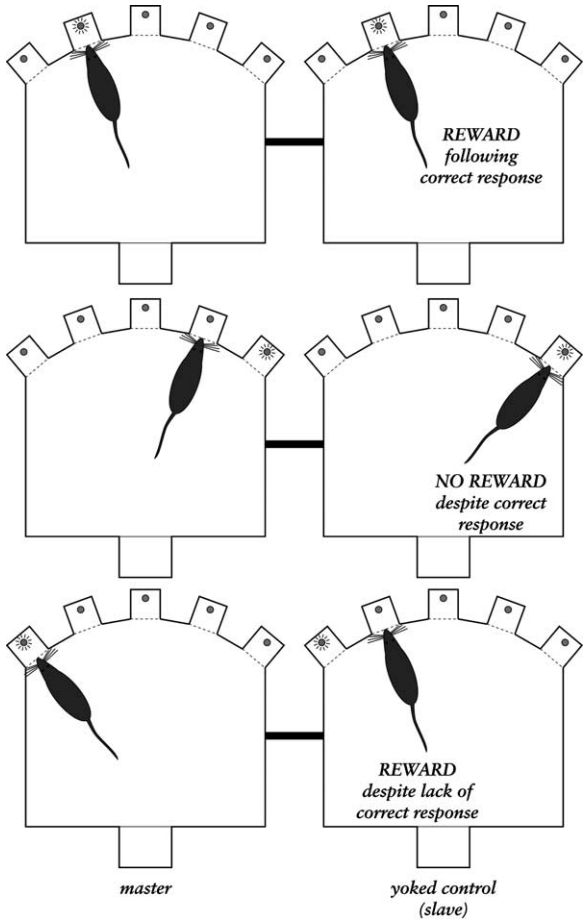

Fig. 4. Degrading the instrumental contingency within the 5-CSRTT (see [30]). Rats are trained on the task and then assigned to pairs. Master rats perform the task as normal. Yoked control (slave) rats experience the stimuli and rewards being earned by the corresponding master animal; their own actions have no consequences. The action–outcome contingency is therefore maintained for the master, but severely degraded for the slave (some examples are illustrated), even though both animals experience identical presentations of stimuli and rewards.

8. Impulsive choice and the prefrontal cortex

8.1. Choice impulsivity: choice involving delayed reinforcement

While the 5-CSRTT assesses one form of impulsivity (i.e. the inability to inhibit a pre-potent motor response in the anticipation of food reward [113]), there are many doubly dissociable kinds of behaviour that may be described as impulsive [50]. Another is impulsive *choice*, a decision-making deficit that may be exemplified by the tendency of an individual to choose an immediate, but small reward, in preference to a larger but delayed reward [2,50,81,87,88,108]. Clearly, impulsive choice may reflect reduced efficacy of delayed reinforcement. It has been considered a normal human characteristic, but impulsive choice contributes to deleterious states such as drug addiction [11,49,65,86,104] and has been suggested to underlie a number of other clinical disorders, including ADHD [116,117]. There are

several animal models of impulsive choice [50,82,108]. In the one that has been most used to study the neuroanatomical basis of impulsive choice, rats are offered repeated choices between an immediate, small reinforcer and a large, delayed reinforcer in discrete trials, with the delay to the large reinforcer being increased as the session progresses [22,51].

8.2. Perigenual anterior cingulate cortex

Although ACg lesions can promote 'motor impulsivity', exemplified by premature responding in the 5-CSRTT [93], and perhaps by over-responding to unrewarded stimuli in other paradigms [16,20,23,97], perigenual ACg lesions have no effect on impulsive choice involving delayed reward [21]. Such a dissociation is not in itself unexpected, as motor impulsivity and impulsive choice have been dissociated before [50]. In this paradigm [21], subjects chose between reinforcers that differed in magnitude and delay (small immediate versus large delayed), but did not differ in probability (both were certain) or response effort. In contrast, it has been found recently that large mPFC lesions encompassing PrL, IL, Cg1, and Cg2 altered rats' preference when the two alternatives differed in magnitude, response effort and delay [124]. Subjects were offered the choice of running down an alley to obtain two pellets or climbing over a steep ramp to obtain four pellets. Large mPFC lesions substantially increased rats' preference for the small-reward, low-effort alternative. Nevertheless, mPFC-lesioned subjects were capable of surmounting the obstacle if there was no low-effort alternative, and their decisions were flexible in that they responded to alterations in either the cost (effort) or the benefit for the alternatives. This effect has since been localized to the ACg [126]; lesions of the PrL and IL have no effect on this task.

8.3. Medial prefrontal cortex

In rats performing the delayed reinforcement choice task [21], lesions of the mPFC have been found to 'flatten' the within-session shift from the large to the small reward; the mean preference for the large reward was *less* than that of shams at zero delay, but *more* than that of shams at the maximum delay [21]. There is no obvious explanation for this effect within theories of choice of delayed reinforcement, implying that the mPFC lesion produced some form of insensitivity to the contingencies or stimuli present in the task. One interpretation is that mPFC lesions disrupted the control over behaviour by the passage of time in each session. There is strong evidence that normal rats learn a session-wide temporal discrimination in this task, and that this temporal discriminative stimulus comes to control responding—in particular the tendency to shift from the large to the small reward as the session progresses [22]. Disruption of such temporal stimulus control might be expected to produce a flattening of the within-session shift of the kind seen. Indeed, aspirative lesions of the mPFC have previously been shown to induce a general deficit in timing ability in rats [47]; lesioned subjects showed a temporal discrimination function that was less steep than normal in the peak procedure, an operant task that assesses the ability to time a discriminative stimulus [24,111]. There is additional evidence that ACg lesions impair timing on the 5-CSRTT during the anticipation of food reward [27,100].

Although there are few published data on the neurochemistry of impulsive *choice* and the prefrontal cortex, a recent unpublished study (Winstanley CA, Dalley JW, Theobald DEH, Cardinal RN, Robbins TW) using in-vivo microdialysis in rats performing a delay-of-reward task suggests that both 5-HT and DA levels increase in the PrL during the delay period. This is clearly of interest because in other settings of impulsivity, namely a one-choice variant of the 5-CSRTT, 5-HT release in this region is unaffected by performance, although individual levels are related to individual differences in impulsive responding [31]. Thus, the ascending 5-HT systems may have a greater functional diversity and specificity than hitherto assumed by the neurobiological organization of this system, and this may be relevant to the various types of impulsive behaviour now identified [49,50].

8.4. Orbitofrontal cortex

Orbitofrontal lesions have produced both impulsive choice [88] and self-controlled choice [129] in very similar paradigms. This apparent discrepancy requires explanation; one possible reason is that in the study of Mobini et al. [88], rats were offered a choice between a 1-pellet immediate reinforcer and a 2-pellet delayed reinforcer, whereas Winstanley et al. [129] used a 1-pellet immediate reinforcer and a 4-pellet reinforcer. Differences in subjects' sensitivity to either the delay or the magnitude of reinforcement can play a role in determining preference in this task [23,67] and it may be that OFC lesions affect both of these parameters [74,88].

9. Synthesis and theoretical considerations

As will be evident from this review, the prefrontal cortex is a widely inter-connected collection of functionally specialized sub-regions involved in the memory, execution and control of adaptive goal-directed behaviour. Although there is a long-standing debate over the existence of a prefrontal cortex in rats, especially an area homologous to the primate dorsolateral prefrontal cortex [105], it is nevertheless encouraging that certain cognitive and executive processes are evidently conserved across different species [13]. The prefrontal cortex is apparently necessary for working memory processes, whether in the spatial or non-spatial domain [5,14,15,34,52,58,70,72,73,79,94,118,120,129], but it is not always clear how deficits on

delayed-response tasks such as delayed alternation or delayed matching relate to mnemonic processes. It is assumed that working memory provides a temporary representation of a stimulus or motor event [76], but neither the PrL nor the ACg appear necessary for the active storage of information relevant to a subsequent delayed response [118]. This implies, in the rat at least, that the medial prefrontal cortex is needed to retrieve or use such information, but not to acquire it. Such a notion fits with the general hypothesis that the prefrontal cortex is involved in different behavioural control processes including, response selection, temporal ordering of events, behavioural flexibility, strategy switching and inhibition of responses that have become pre-potent by their association with reward [33,35,54,71,72,76,100,107]. Response selection processes are subject to inhibition at several levels and there is emerging evidence in rats that these can be functionally localized to different sub-regions of the prefrontal cortex, including the infralimbic and orbitofrontal cortices [12,13,26,27,100].

It has previously been argued that the prefrontal cortex has a 'supervisory' role in maintaining attention, particularly when tasks are non-routine and require constant monitoring of new information to plan appropriate courses of action [119]. Similar functions have been attributed to the rodent medial prefrontal cortex in the context of visual discrimination learning [17] and 'effortful' processing in relation to response selection [58]. An extension of this idea, based on previous theorizing [83] and studies in rodents [10, 30], is that the prefrontal cortex plays a role in contingency perception, or in other words, the detection of predictive relationships between actions and later outcomes to provide a basis for flexible, goal-directed behaviour. Consistent with this hypothesis, lesions of the PrL impair the capacity of rats to perceive action–outcome contingencies [10], whilst degrading the instrumental contingency of the 5-CSRTT in well-trained animals selectively increases NA release in the PrL [30]. Thus, at least some of the functions of the prefrontal cortex involve the integration of acquired relationships and rules based on previous experience and feedback, thus allowing the expression of adaptive goal-directed behaviour in novel circumstances.

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