References

1 Büeler, H. *et al.* (1992) The neuronal cell surface protein PrP is not essential for normal development and behavior of the mouse. *Nature* 356, 577–582
2 Gerlai, R. (1996) Gene-targeting studies of mammalian behavior: is it the mutation or the background genotype? *Trends Neurosci.* 19, 177–181
3 Banbury Conference on Genetic Background in Mice (1997) Mutant mice and neuroscience: recommendations concerning genetic background. *Neuron* 19, 755–759
4 Kelly, M.A. *et al.* (1998) Locomotor activity in D2 dopamine receptor-deficient mice is determined by gene dosage, genetic background, and developmental adaptations. *J. Neurosci.* 18, 3470–3479
5 Bolivar, V.J. *et al.* (2001) Mapping of quantitative trait loci with knockout/congenic strains. *Genome Res.* 11, 1549–1552
6 Gerlai, R. (2001) Null mutant mice: an untapped source of quantitative trait loci. *Trends Neurosci.* 24, 470
7 Dahme, M. *et al.* (1997) Disruption of the mouse L1 gene leads to malformations of the nervous system. *Nat. Genet.* 17, 346–349
8 Magara, F. *et al.* (1999) Genetic background changes the pattern of forebrain commissure defects in transgenic mice underexpressing the β-amyloid-precursor protein. *Proc. Natl. Acad. Sci. U. S. A.* 96, 4656–4661
9 Mineur, Y.S. *et al.* (2002) Behavioral and neuroanatomical characterization of the *Fmr1* knockout mouse. *Hippocampus* 12, 39–46
10 Ivanco, T.L. and Greenough, W.T. (2002) Altered mossy fiber distributions in adult *Fmr1* (FVB) knockout mice. *Hippocampus* 12, 47–54
11 Crabbe, J.C. *et al.* (1999) Genetics of mouse behavior: interactions with laboratory environment. *Science* 284, 1670–1672
12 Van der Staay, F.J. and Steckler, T. (2002) The fallacy of behavioural phenotyping without standardization. *Genes Brain Behav.* 1, 9–13
13 Würbel, H. (2002) Behavioral phenotyping enhanced – beyond (environmental) standardization. *Genes Brain Behav.* 1, 3–8
14 Behringer, R. (1998) Supersonic congenics? *Nat. Genet.* 18, 108
15 Wakeland, E. *et al.* (1997) Speed congenics: a classic technique in the fast lane (relatively speaking). *Immunol. Today* 18, 472–477
16 Mansuy, I.M. *et al.* (1998) Inducible and reversible gene expression with the rtTA system for the study of memory. *Neuron* 21, 257–265
17 Kojima, N. *et al.* (1997) Rescuing impairment of long-term potentiation in *fyn*-deficient mice by introducing *fyn* transgene. *Proc. Natl. Acad. Sci. U. S. A.* 94, 4761–4765
18 Auerbach, W. *et al.* (2000) Establishment and chimera analysis of 129/SvEv- and C57BL/6-derived mouse embryonic stem cell lines. *BioTechniques* 29, 1024–1032
19 Schuster-Gossler, K. *et al.* (2001) Use of coisogenic host blastocysts for efficient establishment of germline chimeras with C57BL/6J ES cell lines. *BioTechniques* 31, 1022–1026
20 Zimmer, A. (1996) Gene targeting and behaviour: a genetic problem requires a genetic solution. *Trends Neurosci.* 19, 470
21 Gerlai, R. (1996) Reply. *Trends Neurosci.* 19, 472
22 Wahlsten, D. (2001) Standardizing tests of mouse behavior: Reasons, recommendations, and reality. *Physiol. Behav.* 73, 695–704
23 Gass, P. *et al.* (1998) Deficits in memory tasks of mice with CREB mutations depend on gene dosage. *Learn. Mem.* 5, 274–288
24 Festing, M.F. *et al.* (1999) Revised nomenclature for strain 129 mice. *Mamm. Genome* 10, 836
25 Montkowski, A. *et al.* (1997) Behavioural performance in three substrains of mouse strain 129. *Brain Res.* 762, 12–18
26 Voikar, V. *et al.* (2001) Strain and gender differences in the behavior of mouse lines commonly used in transgenic studies. *Physiol. Behav.* 72, 271–281
27 Nguyen, P.V. *et al.* (2000) Strain-dependent differences in LTP and hippocampus-dependent memory in inbred mice. *Learn. Mem.* 7, 170–179
28 Balogh, S.A. *et al.* (1999) A behavioral and neuroanatomical assessment of an inbred substrain of 129 mice with behavioral comparisons to C57BL/6J mice. *Brain Res.* 836, 38–48
29 Simpson, E.M. *et al.* (1997) Genetic variation among 129 substrains and its importance for targeted mutagenesis in mice. *Nat. Genet.* 16, 19–27
30 Gerlai, R. (1998) A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. *Behav. Brain Res.* 95, 91–101
31 Wolfer, D.P. *et al.* (1997) Assessing the effects of the 129/Sv genetic background on swimming navigation learning in transgenic mutants: a study using mice with a modified β-amyloid precursor protein gene. *Brain Res.* 771, 1–13
32 Wahlsten, D. *et al.* (2001) Behavioural testing of standard inbred and 5HT(1B) knockout mice: implications of absent corpus callosum. *Behav. Brain Res.* 125, 23–32
33 Carlson, S. and Willott, J.F. (1996) The behavioral salience of tones as indicated by prepulse inhibition of the startle response: relationship to hearing loss and central neural plasticity in C57BL/6J mice. *Hear. Res.* 99, 168–175

David P. Wolfer
Hans-Peter Lipp*
Institute of Anatomy and Center for Neuroscience, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland.
*e-mail: hplipp@anatom.unizh.ch

Wim E. Crusio
Brudnick Neuropsychiatric Research Institute, Dept of Psychiatry, University of Massachusetts Medical School, 303 Belmont Street, Worcester, MA 01604, USA.

Rodent models of prefrontal cortical function

Verity J. Brown and Eric M. Bowman

In this article, we consider whether studies in rats can provide useful information regarding the debate about the functions of the primate prefrontal cortex. At a superficial level, comparison of regional specializations within the prefrontal cortices of different species suggests functional correspondence. Unfortunately, the nature of functional specialization in primate prefrontal cortex is controversial, and data supporting the idea of homology between specific areas of rat and primate prefrontal cortex are weak. Nevertheless, we argue here that studies of the computational functions within the relatively undifferentiated prefrontal cortex of rats can shed light on processing in primate prefrontal cortex.

If any region of the cerebral cortex is unique to the evolution of primates, then the dorsolateral prefrontal cortex is likely to be it. The human dorsolateral prefrontal cortex is involved in many complex cognitive processes that have been described as ‘executive’ – that is, that they form a control system that coordinates cognitive sub-processes. For example, dorsolateral prefrontal cortex is thought to be involved in working memory and holding task-relevant information ‘on-line’ [1,2], supervisory attentional control [3], reasoning and decision-making [4] and the temporal organization of behaviour [5,6]. Despite the fact that their intellectual functioning seems to be spared, patients with damage to frontal cortex can suffer great personal and social difficulties [7]. Compromised prefrontal function is thought to underlie the myriad of complex cognitive deficits that accompany disorders such as Alzheimer’s disease [8,9], schizophrenia [10,11] and Parkinson’s disease [12,13].

Preuss pointed out that there was an absence of evidence, rather than evidence of an absence, for the rat prefrontal cortex including an area homologous to primate dorsolateral prefrontal cortex [14]. Preuss also noted that it was not necessary to postulate that the rat possessed a homologous area: there are considerable

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anatomical differences between rats and primates and, in contrast to primates, lesions of rat frontal cortex result in memory deficits that are neither profound nor long-lasting. If dorsolateral prefrontal cortex has evolved as a module to perform psychological functions unique to primates, then research in the rat would seem to have little to offer those studying the cognitive neuroscience of the frontal lobe.

Does the rat possess an area of prefrontal cortex that is homologous to the primate dorsolateral prefrontal cortex?

Historically, the prefrontal cortex has been defined by its receipt of projections from the mediodorsal nucleus of the thalamus [15]. In primates, the mediodorsal thalamic nucleus sends projections to dorsolateral, medial and orbital surfaces of the frontal lobe. In rats, the mediodorsal nucleus sends projections to the medial and orbital surfaces, but not to dorsolateral regions. Thus, although medial and orbital cortices of the rat fulfil the hodological definition of prefrontal cortex, no area of rat frontal cortex fulfils the gross anatomical position occupied by primate dorsolateral prefrontal cortex. The key question of this article is whether functions equivalent to those of the primate dorsolateral prefrontal cortex are distributed in the medial or orbital regions of the frontal lobe in rats. Recent reviews suggest that the prefrontal cortex on the medial surface of the rat brain is anatomically related to prefrontal cortex on the medial surface of primate brain [16,17]. However, upon reviewing behavioural and anatomical evidence, Kolb suggested that the medial wall cortex of the rat brain is ‘undifferentiated’ prefrontal cortex, and that this area might subserve cognitive functions localized to the dorsolateral prefrontal cortex in primates [18].

Preuss dismissed the functional similarities between rodent and primate prefrontal cortex on the basis of only one behavioural task (the delayed-response task). The prefrontal cortex of primates is involved in many other functions and there are many similarities between the medial prefrontal cortex of rodents and the dorsolateral prefrontal cortex of primates [19]. If the rat demonstrates complex behaviour that requires dorsolateral prefrontal cortex when displayed by primates, then the neural substrate of such behaviour could be regarded as analogous, if not homologous, to dorsolateral prefrontal cortex. Thus, studies in rats might offer much to the controversies surrounding the functions of primate prefrontal cortex.

Is it useful to compare the functions of rat prefrontal cortex with primate dorsolateral prefrontal cortex?

There are inherent difficulties in using rodents as a model of primate dorsolateral prefrontal function. First, the precise computational functions of primate dorsolateral prefrontal cortex are disputed – although nobody disputes their overall complexity. Second, this complexity makes interpretation and modeling of primate dorsolateral prefrontal function problematic: impairment of a fundamental cognitive process might result in impairment of seemingly disparate tasks. Third, some functions of frontal cortex are species-specific (language and verbal reasoning being the most obvious examples). However, identifying functions of frontal cortex in one species could allow the extrapolation of common mechanisms to the frontal cortices of other species. In this sense, studies of rat prefrontal cortical function do not model primate prefrontal cortical function *per se*, but form a separate line of investigation that will, it is hoped, converge with research in primates.

The design of species-appropriate measurements requires careful consideration of the underlying mental operations. Behaviours that are superficially similar in different species need not be mediated by the same cognitive operations (e.g. a person and a parrot saying ‘Hello, Polly’). Conversely, the same cognitive operations and analogous neural substrates could mediate behaviours that appear to differ across species. Therefore, it is important not to be taken in by behaviour that merely looks the same, but to identify common fundamental operations tested under species-appropriate conditions.

Many studies of prefrontal cortical function in the rat have investigated impairment of working memory [19]. Profound working memory deficits following dorsolateral prefrontal cortical damage in humans and electrophysiological investigations in monkeys [20] have confirmed the importance of dorsolateral prefrontal cortex in working memory processes. Nevertheless, at least some of the impairments in learning and memory reported in rats could reflect problems in shifting strategies, rather than the learning of stimulus–response associations *per se* [21]. For example, rats learning a ‘match-to-position’ rule must overcome a spontaneous alternation strategy. Thus, it is recognized that behavioural deficits following prefrontal cortical damage in rats could reflect impaired behavioural flexibility similar to that reported in primates [18,19,22,23].

Impairments of selective attention following medial prefrontal cortical lesions in rats have similarly been interpreted not as purely attentional deficits, but as problems with behavioural flexibility. The most popular task used to demonstrate selective attention in rats is the five-choice serial reaction time task [24]. The rat is presented with a visual cue in one of up to five possible locations and the attentional load is manipulated by varying the duration of stimulus presentation or the number of possible stimulus locations. Rats with lesions of medial prefrontal cortex perform as well as control rats when there are only two potential stimulus locations, even when the stimulus duration is brief [25]. However, when the attentional load is increased (e.g. a choice of up to five possible target locations) medial frontal lesioned rats are less able to detect targets [26]. The patterns of errors in these and other attentional tasks have been interpreted as inconsistent with perceptual attentional difficulties, and taken instead to indicate a deficit in behavioural flexibility [27]. Similarly, a deficit in behavioural flexibility has been suggested to account for impairments in reversal learning of stimuli that are difficult to discriminate [28], delayed response tasks [29] and deficits in ‘effortful processing’ [30] following medial prefrontal cortex lesions in rats. The hypothesis has been more directly tested in studies that examine rats’ ability to shift between response rules [21,23,31–33]. Kesner expresses this as behaviour based on ‘higher order’ rules: namely, the abstraction of associations to make rules and use strategies that make working memory possible [19].

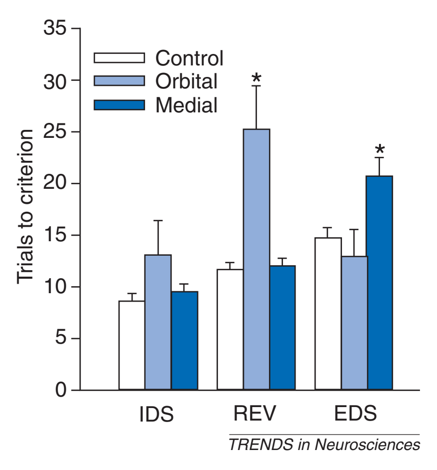

Fig. 1. Number of trials to reach criterion (six consecutive correct trials) for acquisition of an intradimensional new discrimination (IDS), reversal of that discrimination (REV) and acquisition of an extradimensional new discrimination (EDS). Error bars, ± 1 SEM. Rats with lesions centred on the medial prefrontal cortex (prelimbic area PL [42]; $n = 12$) were selectively impaired (*$P < 0.05$) on the extradimensional discrimination compared to controls ($n = 12$) (data replotted from Ref. [39]). Rats with orbital prefrontal cortical lesions (made by infusion of the excitotoxin ibotenic acid into the VLO/VO (ventrolateral orbital/ventro-orbital)area [42], at a position 4.0 mm anteroposterior and ±2.0 mm mediolateral from the Bregma, and 4.5 mm dorsoventral from the skull surface; $n = 6$) showed impaired reversal learning (*$P < 0.05$). However, intra- and extradimensional new acquisition was unimpaired (V.J. Brown and K. McAlonan, unpublished). These data replicate the dissociation reported by Dias *et al.* in marmosets with lesions of lateral and orbital prefrontal cortices [36].

The highest order abstraction is epitomized in the abstraction of rules for guiding behaviour in the Wisconsin Card Sort Test [34], which is impaired by lesions of the dorsolateral prefrontal cortex in human neurological patients. The essence of the impairment is an impediment in shifting of attention from one perceptual aspect of a complex stimulus (such as colour) to another aspect of the stimulus (such as form). This is captured in the ID–ED (intradimensional–extradimensional) task, an analogue of the Wisconsin Card Sort Test that has been used in monkeys as well as in humans [35–38]. The task compares the rate of acquisition of two discriminations, each with stimuli that are novel to the subject, with the only difference between them being whether the preceding discrimination was based on the same stimulus features (an intradimensional shift) or different stimulus features (an extradimensional shift). Stimulus features are often visual properties, but this is not necessarily the case – rules can also be abstracted on the basis of features in other sensory modalities or even those in semantic categories. Acquisition of the new discrimination is less rapid if attention must be redirected to a previously unattended stimulus feature. Lesions of dorsolateral prefrontal cortex in humans [35] or lateral prefrontal cortex in marmoset monkeys [36–38] do not render the subjects unable to learn new discriminations, but acquisition of the extradimensional shift is slower than in controls. By contrast, lesions of orbital prefrontal cortex impair reversal learning [36]. The task is not a delay-dependent test, nor does it load particularly on working memory.

Birrell and Brown designed an attentional set-shifting task that is formally the same as one used in monkeys and humans [39]. Rats are trained to dig in bowls for a food reward. The bowls are presented in pairs, only one of which is baited: the rat must select the bowl in which to dig according to an aspect of its physical characteristics, such as the odour, the digging-medium that fills the bowl or the texture that covers its surface. In a single session, rats perform a series of discriminations that include reversal learning, an intradimensional shift and an extradimensional shift. Rats learn the discriminations readily and show more rapid learning of new discriminations when their attention is already focused on the relevant dimension (intradimensional shift) compared to when a previously irrelevant dimension is made relevant (extradimensional shift). This demonstration provides direct evidence that a rat – just like a monkey or human – is capable of extracting stimulus features to form higher order rules. Lesions of either the medial or the orbital rat prefrontal cortex resulted in different deficits, in a manner strikingly similar to the pattern of deficits seen in marmosets with lesions of lateral or orbital prefrontal cortex: lesions of medial prefrontal cortex impaired the ability to shift attentional set [39], whereas lesions of orbital cortex impaired reversal learning (Fig. 1). As seen in marmosets and in humans, the abilities to shift attentional set and to reverse stimulus–reward associations depend on specific and distinct regions of prefrontal cortex. If the medial prefrontal cortex of the rat is not the anatomical equivalent of dorsolateral prefrontal cortex [14], then the demonstration that it mediates the same kind of processes leads us to consider the nature of functional specializations within different areas of prefrontal cortex.

Is primate dorsolateral prefrontal cortex functionally unique?

The functional specificity of regions of prefrontal cortex could arise from the nature of the information available to the different regions (informational or domain specificity), rather than from regional differences in information processing (processing specificity). There are many alternative suggestions about the precise nature of common processing throughout prefrontal cortex. For example, Goldman-Rakic emphasizes 'domain specific on-line memory' [1]. Similarly, O'Reilly *et al.* [40] propose 'activation based working memory', but further suggest it is the 'level of abstraction' of representations (as opposed to the modality or domain of information) that distinguishes dorsolateral prefrontal from orbital prefrontal cortex. Shimamura's 'dynamic filtering' hypothesis [41] includes working memory as one component of prefrontal cortical processing but, as with the idea of level of abstraction, also goes further. This hypothesis suggests there are four hierarchically organized elements of executive control: selecting (selective attention); maintaining (short-term or working memory); updating (manipulating the contents of working memory or attention monitoring); and re-routing (shifting attention). These analyses all assume that common processing mechanisms are recruited throughout the prefrontal cortex of the primate brain according to task demands, with regional and sub-regional domain specificity. If true, it would be parsimonious to extend this to other mammalian brains.

The conclusion to be drawn from these findings is that it is not necessary to postulate the existence of an area of rat prefrontal cortex that is as anatomically specialized as the human dorsolateral prefrontal cortex. Nevertheless, a functional equivalent might be present if all areas of prefrontal cortex share common processing mechanisms. Studies with rats could confirm the view that prefrontal regional and sub-regional specialization is not necessarily with respect to functional cognitive modules, but reflects instead domain-specificity [1] or level of abstraction [40]. The research in rats need not be so concerned with justifying the behaviour of animals in terms of its similarity to human executive function, as animal-like executive functions are sufficient. Studies of nonprimate species provide a cognitively less complex case, in which the elemental psychological and neural processes in prefrontal cortex can be examined, and from which the functions of human dorsolateral prefrontal cortex can be extrapolated.

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References

1 Goldman-Rakic, P.S. (1987) Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory. In *Handbook of Physiology, The Nervous System, Higher Functions of the Brain, I: V* (Plum, F., ed.), pp. 373–417, American Psychological Society

2 Kinberg, D.Y. and Farrah, M.J. (1993) A unified account of cognitive impairments following frontal lobe damage: The role of working memory in complex organised behaviour. *J. Exp. Psychol.* 122, 411–428

3 Shallice, T. and Burgess, P. (1998) The domain of supervisory processes and the temporal organisation of behaviour. In *The Prefrontal Cortex: Executive and Cognitive Functions* (Roberts, A.C. *et al.*, eds), pp. 22–35, Oxford University Press

4 Damasio, A.R. (1998) The somatic marker hypothesis and the possible functions of the prefrontal cortex. In *The Prefrontal Cortex: Executive and Cognitive Functions* (Roberts, A.C. *et al.*, eds), pp. 36–50, Oxford University Press

5 Fuster, J.M. (1980) *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe*, Raven Press

6 Fuster, J.M. (2000) The prefrontal cortex of the primate: a synopsis. *Psychobiology* 28, 125–131

7 Damasio, A.R. (1994) *Descartes' Error: Emotion, Reason, and the Human Brain*, Grosset/Putnam

8 Kalaria, R.N. and Andorn, A.C. (1991) Adrenergic-receptors in aging and Alzheimers disease – decreased alpha-2-receptors demonstrated by [H-3] P-aminoclonidine binding in prefrontal cortex. *Neurobiol. Aging* 12, 131–136

9 Akbarian, S. *et al.* (1995) Editing for an AMPA receptor subunit RNA in prefrontal cortex and striatum in Alzheimer's disease, Huntingtons disease and schizophrenia. *Brain Res.* 699, 297–304

10 Weinberger, D.R. and Berman, K.F. (1998) Prefrontal function in schizophrenia: confounds and controversies. In *The Prefrontal Cortex: Executive and Cognitive Functions* (Roberts, A.C. *et al.*, eds), pp. 165–180, Oxford University Press

11 Frith, C. (1998) The role of the prefrontal cortex in self-consciousness: the case of auditory hallucinations. In *The Prefrontal Cortex: Executive and Cognitive Functions* (Roberts, A.C. *et al.*, eds), pp. 181–194, Oxford University Press

12 Muller, U. *et al.* (2000) Striatal [I-123]beta-CIT SPECT and prefrontal cognitive functions in Parkinson's disease. *J. Neural Transm.* 107, 303–319

13 Tsuchiya, H. *et al.* (2000) Impaired novelty detection and frontal lobe dysfunction in Parkinson's disease. *Neuropsychologia* 38, 645–654

14 Preuss, T.M. (1995) Do rats have prefrontal cortex? The Rose–Woolsey–Akert Program reconsidered. *J. Cogn. Neurosci.* 7, 1–24

15 Rose, J.E. and Woolsey, C.N. (1948) The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. *Res. Publ. Assn. Nerv. Dis.* 27, 210–232

16 Uylings, H.B.M. and Van Eden, C.G. (1990) Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Prog. Brain Res.* 85, 31–62

17 Groenewegen, H.J. and Uylings, H.B.M. (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog. Brain Res.* 126, 3–28

18 Kolb, B. (1990) Prefrontal cortex. In *The Cerebral Cortex of the Rat* (Kolb, B. and Tees, R.C., eds), pp. 437–458, MIT Press

19 Kesner, R.P. (2000) Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology* 28, 219–228

20 Miller, E.K. (2000) The prefrontal cortex and cognitive control. *Nat. Rev.* 1, 59–65

21 Ragozzino, M.E. *et al.* (1999) Involvement of the prelimbic–infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *J. Neurosci.* 19, 4585–4594

22 de Bruin, J.P.C. *et al.* (1994) A behavioural analysis of rats with damage to the medial prefrontal cortex using the Morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation. *Brain Res.* 652, 323–333

23 Joel, D. *et al.* (1997) Electrolytic lesions of the medial prefrontal cortex in rats disrupt performance on an analog of the Wisconsin Card Sorting Test, but do not disrupt latent inhibition: Implications for animal models of schizophrenia. *Behav. Brain Res.* 85, 187–201

24 Carli, M. *et al.* (1983) Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. *Behav. Brain Res.* 9, 361–380

25 Granon, S. *et al.* (1998) Evidence for the involvement of the rat prefrontal cortex in sustained attention. *Q. J. Exp. Psychol.* 51, 219–233

26 Muir, J.L. *et al.* (1996) The cerebral cortex of the rat and visual attentional function: Dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cereb. Cortex* 6, 470–481

27 Miner, L.A.H. *et al.* (1997) Effects of ibotenic acid-induced loss of neurons in the medial prefrontal cortex of rats on behavioral vigilance: Evidence for executive dysfunction. *J. Psychopharm.* 11, 169–178

28 Bussey, T.J. *et al.* (1997) Triple dissociation of anterior cingulate, posterior cingulate, and medial frontal cortices on visual discrimination tasks using a touchscreen testing procedure for the rat. *Behav. Neurosci.* 111, 920–936

29 Delatour, B. and Gisquet-Verrier, P. (1999) Lesions of the prelimbic–infralimbic cortices in rats do not disrupt response selection processes but induce delay-dependent deficits: Evidence for a role in working memory? *Behav. Neurosci.* 113, 941–955

30 Granon, S. *et al.* (1994) Effortful information processing in a spontaneous situation by rats with medial prefrontal lesions. *Behav. Brain Res.* 78, 147–154

31 Brito, G.N.O. and Brito, L.S.O. (1990) Septohippocampal system and the prelimbic sector of frontal-cortex – a neuropsychological battery analysis in the rat. *Behav. Brain Res.* 36, 127–146

32 Seamans, J.K. *et al.* (1995) Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. *Behav. Neurosci.* 109, 1063–1073

33 Ragozzino, M.E. *et al.* (1999) Involvement of rodent prefrontal cortex subregions in strategy switching. *Behav. Neurosci.* 113, 32–41

34 Milner, B. (1963) Effects of different brain lesions on card sorting; the role of the frontal lobes. *Arch. Neurol.* 9, 90–100

35 Owen, A.M. *et al.* (1991) Extra-dimensional versus intra-dimensional set shifting performance following frontal-lobe excisions, temporal-lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* 29, 993–1006

36 Dias, R. *et al.* (1996) Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 380, 69–72

37 Dias, R. *et al.* (1996) Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behav. Neurosci.* 110, 872–886

38 Dias, R. *et al.* (1997) Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: Restriction to novel situations and independence from 'on-line' processing. *J. Neurosci.* 17, 9285–9297

39 Birrell, J.M. and Brown, V.J. (2000) Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J. Neurosci.* 20, 4320–4324

40 O'Reilly, R.C. *et al.* (2002) Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. *Cereb. Cortex* 12, 246–257

41 Shimamura, A.P. (2000) The role of the prefrontal cortex in dynamic filtering. *Psychobiology* 28, 207–218

42 Paxinos, G. and Watson, C. (1997) *The Rat Brain in Stereotaxic Coordinates* (3rd edn), Academic Press

Verity J. Brown*
Eric M. Bowman
School of Psychology, University of
St Andrews, St Andrews, UK KY16 9JU.
*e-mail: vjb@st-and.ac.uk