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CHAPTER 25

Animal models for human PFC-related disorders

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Introduction

The publication of the *Descent of Man* by Darwin in 1871 can probably be taken as the beginning of the general use of nonhuman subjects to study psychological processes in humans. Darwin argued that human and animal minds were similar and that differences were quantitative, not qualitative. Thus, for Darwin there was a continuum of mental complexity; humans differed in degree but not in kind from other animals. As comparative neurology developed in the decades following Darwin's book, anatomists were struck by similarities across mammalian species, with the principal difference appearing to be the volume of neocortex. The implications of this difference remained uncertain, however, and in his discussion of the differences in the brains of rats and humans C. Judson Herrick remarked that "Rats are not men . . . Men are bigger and better than rats" (Herrick, 1926, p. 365)!

Today, we recognize that although the mammalian cortex is remarkably similar in structure across species (e.g. Rockel et al., 1980), there are significant differences both in the details and in the complexity of the organization of mammalian brains. For example, although there are multiple representations of the sensory inputs in the cortex of all mammals the number of cortical regions, as well as the details of their connections and functions, appear to differ in even relatively closely related species such as Old World and New World monkeys (e.g. Kaas, 1987). The problem is to know when it is reasonable to generalize and when it is not. For behavioural neuroscientists this problem concerns not only the issue of structural equivalence across different brains, but also that of behavioural equivalence in different species.

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Principles underlying interspecies comparisons

The chief purpose of cross-species comparisons in neuroscience has been to understand the basic mechanisms of brain function. In this type of comparative work, the species chosen for study depend upon the nature of the question asked. For example, neurophysiologists may choose to study the neural activity of giant nerve fibres in the squid because the nerve is so large and accessible. Similarly, the barrel fields of the rat cortex may be chosen as a model of cortical function because of their elegant structural organization, which is closely tied to peripheral structure. In both cases there is a clear rationale for why subjects are being chosen and what basic mechanism is under study. Studies of basic mechanisms of frontal lobe function are of a different class, however, since the research questions are tied to a clearly defined structure, namely the frontal lobe. When looking at the basic mechanisms of frontal lobe function it seems reasonable to compare animals with large frontal lobes, such as nonhuman primates, but it is

not clear what the rationale would be for using carnivores or rodents. Their frontal areas are far smaller and it is not clear what "basic mechanisms" one would study in nonprimates. Indeed, a perusal of the literature on the effects of frontal lobe lesions in nonhuman primates suggests that those who study primates have this view and find little of interest in the work on other species since nonprimate work is virtually never cited by these researchers.

A second type of comparative study is designed to describe the phylogenetic development of the brain and to demonstrate the phylogenetic development of humanoid intelligence. In these studies, species are chosen because of a presumed phylogenetic relationship. For example, Masterton and Skeen (1972) selected hedgehogs, tree shrews, and bushbabies as experimental animals solely on the basis of paleontological conclusions regarding their successive common ancestry with anthropoids. The authors then chose to study the animals' capacity to perform a delayed alternation task. They suspected that this test would be a behavioural indicator of the function of the prefrontal system because the prefrontal system is necessary for normal performance of delay-type tasks in anthropoids. The results showed a clear relationship between relative volume of prefrontal cortex (and associated regions including nucleus medialis dorsalis and caudate nucleus), performance on the delayed alternation task, and phylogenetic status (Fig. 1). The results suggest that the capacity to perform delayed alternation-type tests has developed in parallel with the prefrontal cortex and could imply that this ability may be fundamental in the development and function of the prefrontal cortex. On the other hand, the improvement in delayed alternation performance also may be related to the general increase in brain size across these species or to some other factor. Hence, it will be necessary to study the performance of these species on other putative tests of anthropoid frontal lobe function but this has not yet been done. In the long run the difficulty, of course, is in deciding what the appropriate behavioural tests should be. One way to approach this problem is to try to establish behavioural homologies but this is fraught with difficulties. Most definitions of homology are versions of Simpson's (1961) definition of structural homology as resemblance due to inheritance from com-

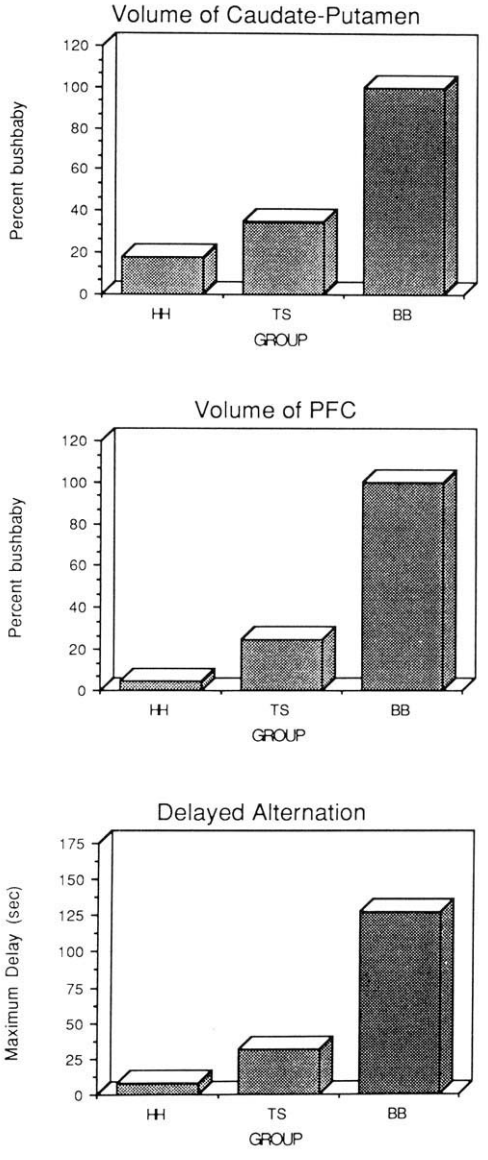

Fig. 1. Comparison of (1) the volume of caudate-putamen and prefrontal cortex and (2) maximum delays on a delayed alternation test in which performance exceeded chance in hedgehogs (HH), tree shrews (TS), and bushbabies (BB). (After Masterton and Skeen, 1972.)

mon ancestry. Atz (1970) applied this to behaviour when he defined behavioural homology by saying that "to be homologous, two behaviours exhibited by two phylogenetically related forms must have been present as a single behaviour in a common ancestor". Such a definition of homology is not too helpful since behaviour leaves no fossil record and it must therefore be tied to decisions regarding structural homology. Furthermore, it is difficult to see how behavioural homology could be established for most behaviours in existing mammals since the common ancestors are so distant. More recent attempts at determining behavioural homology do not really solve this problem (e.g. Hodos, 1976) so it remains difficult to determine the basis for phylogenetic studies of frontal lobe function, except in the limited sense of the Masterton and Skeen type of experiment.

A third approach to comparative studies is to model cerebral organization by placing emphasis upon function rather than structure. The logic of this approach is that although the details of behaviour may differ somewhat, mammals share many similar behavioural traits and capacities that have a similar function. All mammals must detect and interpret sensory stimuli, relate this information to past experience, and act appropriately. Similarly, all mammals appear to be capable of learning complex tasks under various schedules of reinforcement (Warren, 1977) and all mammals are mobile and have developed mechanisms for navigating in space. Although the details of the behaviours vary considerably the general capacities are common to all mammals. Warren and Kolb (1978) proposed that behaviours and behavioural capacities demonstrable in all mammals could be designated as *class-common* behaviours. In contrast, behaviours that are unique to a species and that have presumably been selected to promote survival in a particular niche are designated as *species-typical* (or species-specific) behaviours. Consider the following example.

In our studies of the effects of prefrontal lesions upon the social behaviour of cats we considered the response of cats to species-typical releasers, namely urine and the posture of conspecifics. Urine is used as a territorial marker by cats, who spray distinctive landmarks, such as bushes, large rocks, posts, or walls with a fine mist of urine. Other cats exhibit a striking behavioural sequence, known as flehmen, when they encounter the urine of a conspecific (Kolb and Nonneman, 1975). The most common components of the response pattern include approaching, sniffing, and touching the urine source with the nose, flicking the tip of the tongue repeatedly against the anterior palate behind the upper incisors, withdrawing the head from the urine, and opening the mouth in a gape or "flehmen response", and licking the nose. This behavioural pattern apparently allows olfactory stimuli to reach the secondary olfactory system, which appears to be specialized to analyse odours that are species-relevant. Cats show this response to urine of other cats, and oddly enough to humans, but they do not show it to urine of rhesus monkeys, dogs, rats, or hamsters. They also do not show it to cat fecal matter or cat fur, although they do show it to cat earwax! Like many mammals, cats are also highly responsive to the sight of conspecifics, and their response is strongly affected by the posture and piloerection of other cats. When we studied the effect of prefrontal lesions upon the responses to urine and to silhouettes of cats in different postures we found that although both normal and frontal cats responded to the stimuli, they did so in different ways (Nonneman and Kolb, 1974). The cats with prefrontal lesions sniffed the urine but showed little interest and showed no flehmen response, which means that the accessory olfactory system did not have access to the odour, and although the frontal cats oriented and piloerected to cats in a "halloween" posture, they did not approach the model. Furthermore, when placed in a large room with a novel cat (who was unoperated) the frontal cats were submissive and attempted to escape from the room whereas the normal cats approached the frontal animals and were generally aggressive. Hence, prefrontal lesions in cats altered the normal response to the species-typical social releasers of urine and

piloerection. These results led me to the conclusion that prefrontal lesions would have the class common effect of altering the normal response to social releasers, which would have the effect of altering social behaviour. To test this idea my colleagues and I did parallel experiments looking at the response of people with unilateral frontal lobe removals to what appeared to be parallel stimuli in people, namely facial expression and tone of voice (prosody). Our results showed that frontal lobe patients were very poor at the recognition of facial expression and prosody (Kolb and Taylor, 1981, 1988).

The results of our studies on cats and humans showed changes in behaviours unique to each species (urine and piloerection in cats and the facial expression and prosody in humans) as well as a change in a more general class of behaviour, which we can call social behaviour. The details of behavioural change to particular stimuli are *species-typical,* the general function of the behaviour changed is *class-common.* It makes little sense to try to study response to flehmen in humans, since humans do not display it, nor to study facial expression in cats, since cats have little facial expression. These behaviours are species-typical. Similarly, it makes little sense to suggest that the prefrontal cortex has a general function in mammals of controlling facial expression or flehmen. Rather, it is more reasonable to conclude that the general function of the prefrontal cortex is to perceive, and perhaps to produce, species-typical social behaviours, of which flehmen and facial expression are examples. The advantage of this approach to comparative studies is that it is possible to make comparisons in species that are not closely related phylogenetically by focussing upon the function of the behaviour in question rather than upon the details of the behaviours.

The distinction between class-common and species-typical behaviours provides a rationale for making cross-species comparisons but it is not without weaknesses of its own (see Kolb and Whishaw, 1983a). In particular, we must ask whether it is legitimate to assume that since behaviours in different species have the same function, the neural substrates of the behaviours are the same. There is certainly no guarantee that just because mammals have class-common behaviours they have not independently evolved solutions to the class-common problems. Within the class Mammalia this seems unlikely, however, as there is little or no evidence in support of convergent evolution of neural substrates of class common behaviours, or at least within the placental mammals. Neurophysiological stimulation, evoked potential, and lesions studies reveal a similar topography in the motor, somatosensory, visual, and auditory cortices of the mammals, a topography that can provide the basis for the class-common neural organization of fundamental capacities in mammals. Kaas (1987) has suggested that all placental mammalian species appear to have several basic cortical regions in common including primary and secondary visual fields, primary and secondary somatosensory fields, at least a primary auditory cortex, a region of posterior temporal cortex with input primary visual cortex, taste cortex, frontal cortex receiving projections from the medialis dorsalis of the thalamus, and several subregions of limbic cortex related to the anterior and lateral dorsal thalamic nuclei. There are certainly significant species differences in cortical organization, however, particularly in (1) the number of cortical fields beyond the common core in each sensory modality, (2) the size of the class-common subfields, and (3) the details of cortico-cortical connections. These interspecies differences can be presumed to contribute to the unique behavioural repertoire that permits different species to survive in its particular niche. The similarities in organization presumably reflect a class-common solution to the problems of being a mammal. It is likely that the prefrontal cortex as a whole will have class-common functions but that in view of the divergent evolution of existing mammalian forms the organization of the subregions with the prefrontal cortex *may* show significant functional differences, in part because a major source of afferents to the prefrontal cortex

is from the various sensory subfields, which themselves show significant cross-species differences in organization.

It will be the goal of the remainder of this chapter to illustrate the class-common functions of the prefrontal cortex of mammals. I shall illustrate the arguments by comparing the anatomical organization of the prefrontal cortex of rodents and primates and then consider the effects of prefrontal lesions in rats, monkeys and humans. I shall argue that there are remarkable parallels in the organization and function of the frontal lobe across the class Mammalia. Further, I will suggest that since species that are markedly divergent both in their level of encephalization and in their ecological adaptations have basic prefrontal functions in common, functions that are likely to be class common. Finally, I will argue that the commonality in function of the prefrontal cortex suggests that much may be learned about the function of the prefrontal cortex by considering it in the context of its biological function in mammals.

Structural comparisons

A primary concern in making cross-species generalizations about prefrontal function is that we are discussing tissue that is structurally equivalent. The traditional way of determining equivalence is to search for homologies. Since brains leave poor fossil records this must be done indirectly. Campbell and Hodos (1970) proposed that similarities in the following criteria could be used to establish homology: (1) connections; (2) topography; (3) position of reliably occurring sulci; (4) embryology; (5) morphology of individual neurones; (6) histochemistry; (7) electrophysiology; and (8) behavioural changes from lesions and stimulation. For the present purposes of comparing rodents and primates I shall focus upon connections.

Thalamo-cortical projections

If we use Rose and Woolsey's (1948) definition of prefrontal cortex as that cortex receiving afferents from medialis dorsalis of the thalamus (MD), then we can identify a region of prefrontal cortex in all mammal brains. In both rodents and primates there is a topographic organization to these projections such that we can identify different cortical subfields (e.g. Divac et al., 1978; Goldman-Rakic and Porrino, 1985). There are difficulties in generalizing from these thalamo-cortical connections, however, since it is now clear that McCulloch's (1944) idea that the principal thalamic nuclei project to separate areas to form a mosaic of functional anatomical areas is in error because thalamic projections are not as discrete as was once believed. For example, in the rat, part of the medial MD projection cortex receives overlapping projections from the medial anterior nucleus (AM), the ventral nucleus (V), or the paratenial nucleus (PT), as well as the lateral posterior nucleus (LP), as illustrated in Fig. 2 (Divac et al., 1978). A parallel pattern of overlapping projections is also seen in the monkey as MD projections overlap with AM and the medial pulvinar nucleus (Goldman-Rakic and Porrino, 1985). Thus, in both species there is frontal tissue receiving only

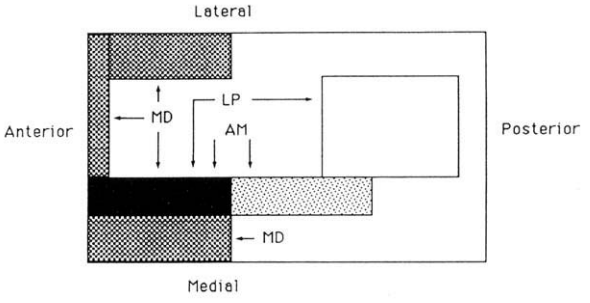

Fig. 2. Schematic illustrations of the types of overlap of thalamic projections to the prefrontal cortex of the rat. The largest rectangle represents the folded-out neocortex of the right hemisphere, with the frontal pole at the top. The checkered area represents the area receiving projections from medialis dorsalis, (MD), ventral tegmentum, and basolateral amygdala; the stippled area represents the area receiving projections from only medialis anterior (AM); the black area represents the area receiving projections from MD, AM, posterior lateralis posterior (LP), basolateral amygdala, and ventral tegmentum. (Adapted from Divac et al., 1978.)

MD projections, tissue receiving MD and AM projections, and tissue receiving projections from the same posterior nucleus that projects to the posterior parietal region. The putative role of posterior parietal cortex in spatial guidance, and the overlapping of posterior parietal thalamic projections (LP/pulvinar) with those of MD and AM in the prefrontal cortex, imply that the prefrontal cortex may be part of a circuit whose function is related to visuospatial guidance.

Cortico-cortical connections

The prefrontal cortex receives two types of cortico-cortical projections: those from sensory regions and those from the posterior parietal area (see Fig. 3). As the prefrontal cortex has expanded in mammalian evolution, the pattern of projections has become more complex: as the sensory areas enlarged and divided into additional sensory fields there has been a corresponding increase in the volume and subregions of the prefrontal cortex (e.g. Petrides and Pandya, 1988). This general pattern of cortico-cortical connections can be seen in both

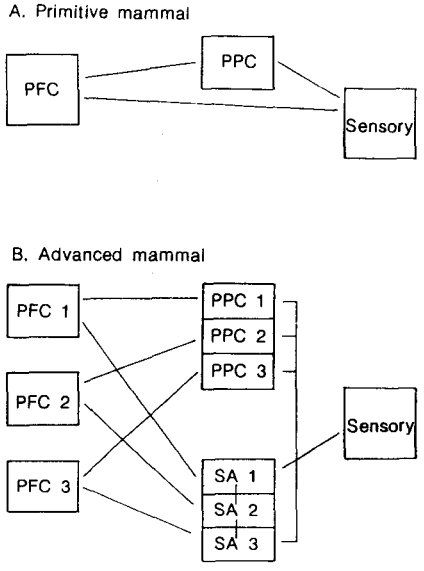

Fig. 3. The putative cortico-cortical connections of the prefrontal cortex of a hypothetical primitive and advanced mammal (e.g. monkey). In the advanced mammal there is an expansion of the posterior parietal region, and the development of the secondary association regions, which replace the primary sensory cortex as the major sensory afferent. Abbreviations: PFC, prefrontal cortex; PPC, posterior parietal cortex. Sensory refers to the visual, auditory and somatosensory cortices. The designations 1, 2 and 3 in the lower panel indicate that there are multiple regions of PFC, PPC and SA cortex.

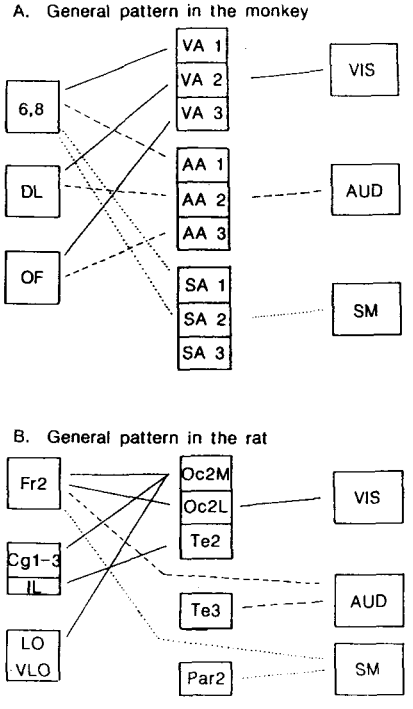

Fig. 4. A comparison of the cortico-cortical connections of the prefrontal cortex of the rhesus monkey and the rat. The details differ but the general principle is similar, except that the rat still has direct primary sensory projections to the prefrontal cortex. (Note: there is also a direct visual-Fr2 projection in the rat that is not shown.) Nomenclature after Pandya and Yeterian (1985) for the monkey and Zilles (1985) for the rat. Abbreviations: AA, auditory association cortex; AUD, primary auditory cortex; Cg1 – 3, cingulate regions 1 – 3; DL, dorsolateral prefrontal cortex; IL, infralimbic cortex; Fr2, frontal cortex, area 2; LO, lateral orbital cortex; Oc2M, medial occipital area 2; Oc2L, lateral occipital area 2; OF, orbital frontal cortex; Par1, 2, parietal areas 1 and 2; SA, somatosensory association cortex; SM, somatosensory cortex; Te1, Te2, Te3, temporal areas 1, 2 and 3; VA, visual association cortex; VIS, visual association cortex; VLO, ventral orbital cortex. The solid, dashed, and dotted lines represent the visual, auditory, and somatosensory regions, respectively.

the rat and monkey, although it is more complex in the monkey. Fig. 4A shows the general organization of sensory projections to the prefrontal regions of the monkey (Pandya and Yeterian, 1985). Each of the visual, auditory and somatosensory regions sends projections from the primary cortex to a series of sensory association zones, which project, in turn, to different prefrontal zones. Fig. 4B summarizes the connections in the rat and it can be seen that although there appear to be fewer secondary sensory zones in the rat, the pattern of connections is strikingly similar to that of the monkey. The one major difference is that there are direct projections from the primary sensory regions, as well as from the secondary regions. Furthermore, the visual inputs appear to be more extensive in the rat than the projections from other cortical areas, whereas in primates there are more equally balanced projections from the visual, auditory, and somatosensory systems.

Fig. 5A summarizes the general pattern of cortico-cortical connections to the posterior parietal cortex in the monkey. This cortex (area PG) receives projections from the visual, auditory and somatosensory regions and, in turn, sends projections to the dorsolateral and periarcuate regions (e.g. Goldman-Rakic, 1987). Again, the pattern of connections in the rat is strikingly similar, although far simpler in detail. There is some debate regarding the nature and position of the posterior parietal cortex of the rat but on the basis of its cytoarchitecture, thalamic connections, cortico-cortical connections, and behavioural changes after lesions, Krieg's area 7 is a likely candidate (Kolb, 1990; Kolb and Walkey, 1987). This region receives projections from visual and somatosensory regions and sends projections to MD projection areas, the heaviest projections being to the orbital region and the frontal eye fields.

In summary, a comparison of the cortico-cortical connections in rodents and nonhuman primates shows a considerable parallel in the general pattern of connections. There are, however, differences in details as the projections are less extensive in the rat.

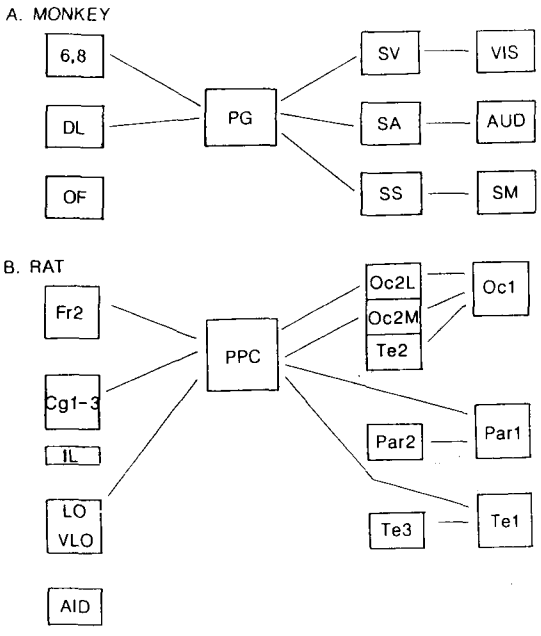

Fig. 5. Connections of the prefrontal and posterior parietal regions of the monkey and rat. Although there a differences, the general pattern is similar. Nomenclature after Pandya and Yeterian (1985) for the monkey and Zilles (1985) for the rat. Abbreviations as in Figs. 3 and 4, and: AID, agranular insular, dorsal, cortex; PG, area PG of the posterior parietal cortex of the monkey; SA, secondary auditory cortex; SS, secondary somatosensory cortex; SV, secondary visual cortex.

Cortico-subcortical connections

In addition to the thalamo-cortical connections there are extensive connections to other subcortical areas in both rodents and monkeys. Table I summarizes these connections and once again, there is a striking parallel. In particular, in both species there is a dopaminergic projection (substantia nigra and ventral tegmental area) and an amygdaloid projection that is coextensive with the MD projections. Every other region that receives prefrontal projections in the monkey also receives projections in the rat, and in addition, the rat receives projections from CA1 of the hippocampus and the nucleus accumbens.

In conclusion, although it is not possible to justify a conclusion that the MD projection cortex

TABLE I

Summary of subcortical connections of prefrontal cortex of monkey and rat

Structure	Monkey	Rat
Amygdala	+	+
Caudate-putamen	+	+
Pretectum, superior colliculus	+	+
Parahippocampal area	+	+
CA1	?	+
Posterior cingulate cortex	+	+
Substantia nigra, VTA	+	+
Nucleus accumbens	?	+
Claustrum	+	+
Hypothalamus	+	+
Mesencephalon	+	+
Pons	+	+

Note: "+" indicates a connection has been demonstrated. For details, see Kolb (1990) and Goldman-Rakic (1987).

of the monkey and the rat is homologous, there can be little doubt that the pattern of cortical and subcortical connections is very similar in general plan in the two species. Although this could be the result of parallel or convergent evolution, it seems more likely that the connections represent a general pattern of prefrontal connections across mammals, possibly resulting from their being present in a common primitive mammalian ancestor. The question we must now address is whether the similarity in structure underlies similarity in function.

Functional comparisons

The oldest and most widely used approach to functional localization in the neocortex is to analyse the behavioural effects of a lesion to circumscribed regions of the neocortex and to compare these effects to those resulting from lesions elsewhere in the cortex. Although the lesion technique is fraught with interpretational problems (see Kolb and Whishaw, 1990, for an extensive discussion), it remains as the major tool of comparative neuropsychology. The major challenge in the current context is to try to identify class-common functions that are disrupted by lesions to the prefrontal cortex of different species. I have grouped the behavioural changes into somewhat arbitrary groups that I believe may measure similar functions in humans, monkeys, and rats. Two difficulties in comparing humans to other species are that (1) the brain lesions in humans are the result of natural events and thus do not correspond to discrete subfields; and (2) the brain lesions in humans are usually unilateral. As we shall see, however, these differences do not appear to lead to major differences in the general pattern of behavioural symptoms (for more details, see Kolb and Whishaw, 1989).

Tables II – IV summarize the general behavioural changes observed after frontal cortex lesions in rodents, monkeys, and humans, respectively. My

TABLE II

Summary of major symptoms of prefrontal cortex damage in rodents

Symptom	Basic reference
1. Poor temporal memory	
a. poor spatial working memory	Kolb et al., 1983
b. poor DNMS	Kolb et al., 1989
c. poor delayed response	Kolb et al., 1974
d. poor habituation	Kolb, 1974b
e. poor associative learning	Passingham et al., 1988
2. Environmental control of behaviour	
a. impaired response inhibition	Kolb et al., 1974
b. alterations in mobility	Kolb, 1974a
c. contralateral neglect	Crowne, 1983
3. Reduced behavioural spontaneity	Kolb and Gorny, 1990
4. Disturbance of motor function	
a. poor execution of chains of movements	Kolb and Whishaw, 1983
b. restricted tongue mobility	Whishaw and Kolb, 1983
5. Impaired spatial orientation	Kolb et al., 1983, 1989
6. Impaired social and sexual behaviour	Kolb, 1974c; Michal, 1973
7. Impaired odour discrimination	Eichenbaum et al., 1980

TABLE III

Summary of major symptoms of prefrontal cortex damage in nonhuman primates

Symptom	Basic reference
1. Poor temporal memory	
a. poor spatial working memory	Passingham, 1985; Funashita et al., 1986
b. poor DNMS	Mishkin and Appenzeller, 1987
c. poor delayed response	Mishkin, 1964
d. poor habituation	Butter, 1964
e. poor associative learning	Petrides, 1982
2. Environmental control of behaviour	
a. impaired response inhibition	Mishkin, 1964
b. alterations in mobility	Gross and Weizkrantz, 1964
c. contralateral neglect	Crowne, 1983
3. Reduced behavioural spontaneity	Myers, 1972
4. Disturbance of motor function	
a. poor execution of chains of movements	Deuel, 1977
b. poor voluntary eye gaze	Latto, 1978
5. Impaired spatial orientation	Mishkin, 1964; Pohl, 1973
6. Impaired social and sexual behaviour	Butter and Snyder, 1972
7. Impaired odour discrimination	Tanabe et al., 1975

review has been selective; the intention was to list representative examples rather than to be comprehensive. I have not concerned myself with lesion locus within the prefrontal cortex, both because of the limited information regarding localization in humans as well as the questions of analogous regions in different species.

Temporal memory

The first evidence that prefrontal lesions might interfere with some type of memory process came from Jacobsen's (1936) discovery of a delayed response deficit in two chimpanzees with frontal lesions. Similar deficits have subsequently been shown in many species ranging from humans (Freedman and Oscar-Berman, 1986) to rats (Kolb et al., 1974). Similarly, there is evidence from studies of both monkeys and rats that prefrontal lesions lead to impairments in "delayed nonmatching-to-sample" tests (Kolb et al., 1989; Mishkin and Appenzeller, 1987) in which animals are shown a cue, and then, after a short delay, are given a pair of stimuli, one identical to the first and one different from it. Animals are rewarded for choosing the novel stimulus. Both rats and monkeys with prefrontal lesions perform as well as con-

TABLE IV

Summary of major symptoms of prefrontal cortex damage in humans

Symptom	Basic reference
1. Poor temporal memory	
a. poor spatial working memory	Corkin, 1965
b. poor recency memory	Milner, 1974
c. poor delayed response	Freedman and Oscar-Berman, 1986
d. poor frequency estimate	Smith and Milner, 1985
e. poor habituation	Luria and Homskaya, 1964
f. poor associative learning	Petrides, 1985
2. Environmental control of behaviour	
a. impaired response inhibition	Milner, 1964
b. alterations in mobility	Ackerly, 1964
c. risk taking and rule breaking	Miller, 1985
d. contralateral neglect	Damasio et al., 1980
3. Reduced behavioural spontaneity	Jones-Gotman and Milner, 1977
4. Disturbance of motor function	
a. poor execution of chains of movements	Kolb and Milner, 1981b
b. poor voluntary eye gaze	Guitton et al., 1982
c. Broca's aphasia	Brown, 1972
5. Impaired spatial orientation	Semmes et al., 1963
6. Impaired social and sexual behaviour	Blumer and Benson, 1975
7. Impaired odour discrimination	Potter and Butters, 1980

trols at short delays, but fail to chance at longer delays (Fig. 6).

The source of the deficits on delay tasks has been controversial, but it would appear that successful performance requires that (1) sensory information be received and appropriately processed, (2) the sensory information must be held "on line" for some temporal interval until a behaviour is produced or a decision reached, and (3) the appropriate response needs to be made. It is the second function that is hypothesized to be dependent upon the prefrontal cortex (e.g. Goldman-Rakic, 1987). This process has been given many labels including short-term memory, representational memory, and a temporary memory buffer (e.g. Goldman-Rakic, 1987; Rawlins, 1985), but the essential idea is that there is a memory process that provides a temporary neural record of stimulus or motor events that occur over time. This allows animals to respond to sensory information after some delay and in the absence of the original stimuli. I shall call this temporal memory.

Although deficits in temporal memory are easily demonstrated in delay-type tasks, temporal memory deficits are also apparent in a variety of other behavioural tasks. For example, a series of studies by Brenda Milner and her colleagues have revealed that frontal lobe patients are unable to keep track of their responses on a variety of tasks (e.g. Petrides and Milner, 1982) or to accurately judge which of two stimuli, which were previously presented, was presented most recently (e.g. Milner, 1974). A further example of a temporal memory deficit may be seen in the process of habituation. Rats, monkeys, and humans with prefrontal cortex lesions all show a retarded habituation to novel stimuli as illustrated for rats in Fig. 7 (see Tables II – IV for references). Finally, animals with prefrontal lesions are impaired at tasks that are often described as "associative". For example, Petrides (1982, 1985) found that both monkeys and humans with prefrontal lesions were impaired at learning to make a particular motor response with distinctive stimuli. Although this deficit is often described as one of association memory, it may be reducable to one of temporal memory since successful solution of the task re-

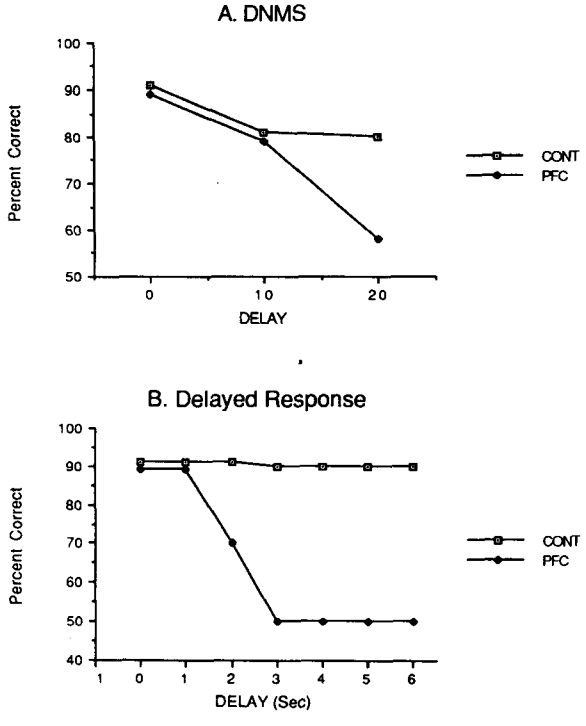

Fig. 6. Summary of delayed nonmatching to sample (DNMS) and delayed response performance of rats with medial prefrontal lesions (PFC). (After Kolb et al., 1974, 1989.)

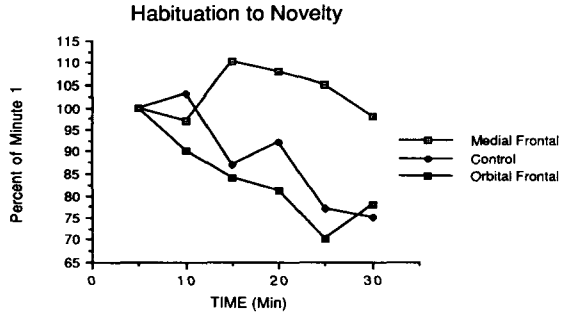

Fig. 7. Change in investigatory behaviour (head poking out of a small hole in a large box) over a 30 min test. Rats with medial frontal lesions did not decline over the test period whereas normal rats and rats with orbital frontal lesions habituated. These data may reflect an absence of normal temporal memory in rats with medial prefrontal lesions. (After Kolb, 1974b.)

quires that the subject keep track of the relationship of a cue and a response, which changes from trial to trial. A failure to keep a temporal record of which combination of response and cue was successful would result in poor performance.

Reduced behavioural spontaneity

One of the common clinical symptoms of patients with frontal lobe lesions is that they seldom spontaneously initiate other than simple behaviours. For example, it is not uncommon for relatives to complain that frontal lobe patients are content to lie in bed, watch television, or just sit. This has been quantified in many ways including tests of verbal fluency (Milner, 1964), facial expression (Kolb and Milner, 1981b), spontaneous speech (Kolb and Taylor, 1981), and doodling (Jones-Gotman and Milner, 1977). With each behaviour, the frontal lobe patients emit fewer behaviours per time unit than do normal controls or patients with lesions elsewhere.

There have not been any systematic attempts to demonstrate similar deficits in other species but at least circumstantial evidence suggests that similar deficits occur. For example, in a recent study of play behaviour in rats with infant frontal lesions Kolb and Gorny (1990) found that although frontal animals were at least as active as control animals, they virtually never initiated play behaviour. Once initiated by a normal animal, however, they did show all the normal components of play behaviour, although again it was less frequent than normal. Similarly, Myers (1972) studied spontaneous vocalizations in monkeys finding a sharp reduction in frontal monkeys. Other lesions did not have this effect. Thus, it appears that the prefrontal cortex plays some role generating novel behaviours. The presence of such a mechanism appears plausible and mammals are characterized by the variability and spontaneity of behaviour. This putative function could also be related to a more general class of behaviours that characterize some forms of "intelligence". Thus, Milner et al. (1985) suggested that the frontal lobe might play some role in what Guilford has termed divergent thinking, which is required to solve open-ended problems such as "How many ways can one use a coat hanger". Frontal lobe patients could be expected to do poorly on such a task, in spite of their normal performance on tests of general intelligence, which tend to test convergent thinking in which there is typically a single answer to the questions posed.

Response to environmental contingencies

A behavioural function that is clearly related to spontaneity is the ability to be flexible when environmental demands change. In contrast to lower vertebrates, mammals have evolved remarkable behavioural plasticity as characterized by the ability to adopt new strategies for problem solving when environmental contingencies change. This flexibility takes many forms including the ability to learn complex associations between seemingly unrelated events (e.g. red means stop), as well as the ability to alter well-learned behaviours when they no longer prove useful. One of the most notorious effects of frontal lobe lesions in mammals is the apparent inability of the subjects to inhibit various types of behaviour. In humans, this can be most clearly shown in tests in which there are specific rules, either implicit or explicit to the task, and failure to respect the rules results in failure at the task. This can be quantified in a number of tests including the Wisconsin Card Sorting Test (e.g. Milner, 1964), and a test of risk taking (Miller, 1985; Miller and Milner, 1985).

Evidence of similar difficulties in nonhuman species comes largely from learning tasks in which the animal is required to learn a particular solution to a problem and then must later make a response that is incompatible with the original learning. Perhaps the best example is spatial reversal learning as rats, cats, dogs and monkeys with frontal lesions are all known to be impaired at such tests.

One of the oldest reported effects of prefrontal lesions in nonhumans is a general increase in activity, which occurs in both monkeys and rats. The

reason for this increased activity is uncertain but it could represent a failure to inhibit movement and/or a failure to generate alternate behaviours. Such increased mobility is rare in human subjects but it may require bilateral lesions to be noticeable. Indeed, case reports of people with large bilateral frontal lesions almost uniformly note the increased activity (e.g. Ackerly, 1964).

Although the source of much debate in the literature, there is another peculiar transient behavioural effect of frontal lesions in rats and monkeys, and perhaps in people: unilateral frontal lesions often produce sensory neglect (e.g. Crowne, 1982). The reason for neglect is controversial but it may represent a change in the animal's ability to recognize environmental change, such that the subject continues to engage in the behaviour ongoing at the time of stimulation. Admittedly speculative, this behavioural loss can thus be seen as part of a more general inability to produce flexible behavioural responses to environmental stimulation.

Disturbances of motor function

Damage to prefrontal areas produces disturbances in the execution of complex movements in humans, monkeys and rats. This behavioural change is sometimes described as a deficit in the programming of chains of movements, or possibly in the planning of movements. For example, Kolb and Milner (Kolb and Milner, 1981a, b; Milner and Kolb, in preparation) found a deficit in the copying of series of movements of either the face or the arms by frontal lobe patients (Fig. 8), which was consistent with blood flow studies by Roland et al. (1980) that found increased blood flow in the supplementary motor area during arm movements. Evidence of parallel deficits in nonhuman subjects has been more indirect, although the symptoms are likely comparable. For example, studies using rats and monkeys have shown deficits in the opening of puzzle latches in animals with prefrontal lesions (e.g. Deuel, 1977; Kolb and Whishaw, 1983b). Further, rats and hamsters with MF lesions are impaired at chaining together the behavioural units required for nest building or maternal behavior (e.g. Kolb and Whishaw, 1985). By filming the nest building behaviour of hamsters we were able to show that the animals are capable of performing each of the individual movements but appear unable to reliably execute the behavioural sequence. Similar behavioural disturbances in humans would probably be called apraxias, but the appropriateness of this term for nonhuman species is open to question.

Social and sexual behaviour

One of the most obvious and striking effects of frontal lobe damage in humans is a marked change in social behaviour and personality. Although most reports have been purely descriptive, recent studies have shown an impairment in the perception of affective states in others (Kolb and Taylor, 1981, 1988), reductions in spontaneous facial expressions (Kolb and Milner, 1981) as well as in the intensity of posed expressions (Kolb and Taylor, 1988), and a tendency toward social isolation (Deutsch et al., 1979). For example, Kolb and Taylor (1988) asked subjects to produce facial expressions that were appropriate for particular characters, who had no facial features, in cartoon sketches of everyday situations (e.g. receiving a

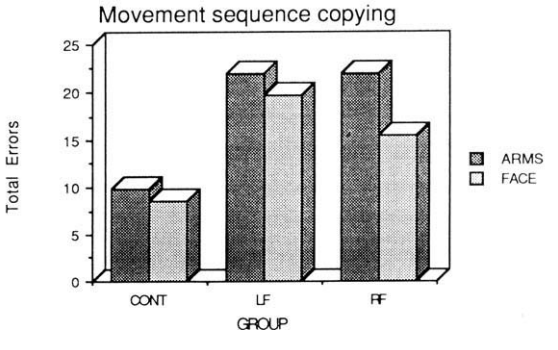

Fig. 8. Summary of arm and facial movement copying deficits in human frontal lobe patients with left or right unilateral frontal excisions. Frontal lobe patients are impaired at both tasks but not at making single movements. (After Kolb and Milner, 1981a.)

traffic ticket). On a subsequent test they were asked to choose an appropriate face for the cartoon character from an array of 6 faces. Frontal lobe patients were impaired at both tests relative to normal controls or patients with temporal lobectomies.

Similarly, monkeys with frontal lobe lesions, especially orbital frontal lesions, have a wide variety of abnormalities in social behaviour. For example, in one study Butter and Snyder (1972) removed the dominant male from each of several groups of monkeys, subsequently removing the frontal lobes from half of the monkeys. When the animals were later returned to their groups they all resumed the position of dominant male, but all of the frontal monkeys were deposed and fell to the bottom of the group hierarchy, although the downfall took varying amounts of time, ranging from a few days to several months. Other studies have shown that like humans with frontal injuries, frontal monkeys do not correctly interpret social displays of others and tend to be social isolates (e.g. Suomi et al., 1970). The social behaviour of both cats and rodents is markedly different from that of primates but we have found that prefrontal lesions in both species disrupt various aspects of social interactions (e.g. Kolb, 1974c; Lubar et al., 1973; Nonneman and Kolb, 1974). As described earlier, cats with frontal lesions do not respond normally to the visual and olfactory cues from other species. Similarly, frontal hamsters do not respond normally to species-typical olfactory cues (Shipley and Kolb, 1977) and rats do not respond normally to tactile cues in social grooming (Kolb, 1974c). Overall, it thus appears that frontal lesions alter the response to species-typical social releasers, which leads to significant changes in social interaction.

Sexual behaviour is presumably social and once again frontal lobe lesions appear disruptive. Complaints about reduced libido are common from relatives of frontal patients, although in some cases right frontal lobe lesions may release sexual activity (e.g. Blumer and Benson, 1975). There are, however, no systematic investigations of sexual behaviour in human frontal lobe patients. Similarly, there are few studies of sexual behaviour in nonhuman subjects with frontal lesions, the principal exceptions being two different reports of altered sexual behaviour in rats with medial frontal lesions (Larsson, 1970; Michal, 1973).

Odour discrimination

Damage to the orbital frontal area of humans, monkeys and rats impairs the ability to discriminate different odours (e.g. Eichenbaum et al., 1980; Potter and Butters, 1980; Tanabe et al., 1975). In addition, the activity of cells in the orbital cortex of the monkey is modulated by specific odours. Taken together, these data suggest that the orbital prefrontal cortex can be considered to be the primary olfactory cortex. The relationship between olfaction and other frontal lobe functions is unclear, however.

Other symptoms of prefrontal lesions

The classical stimulation studies of the 1940s demonstrated that electrical stimulation of at least parts of the prefrontal cortex produced various autonomic effects including changes in respiration, blood pressure, and heart rate (see review by Neafsey, this volume). More recently, there have been several demonstrations of projections from the prefrontal cortex to the vagal solitary nucleus in the medulla of the rat (e.g. Van der Kooy et al., 1982). Similarly, there is evidence that prefrontal lesions reduce food intake in both monkeys and rats, possibly due to drop in "set point" (e.g. Butter and Snyder, 1972; Kolb et al., 1977). The nature of the autonomic functions of the prefrontal cortex is still poorly studied and its relationship to other prefrontal functions is unclear. Nonetheless, there is evidence that such a function exists across mammalian species.

Do frontal lesions produce a deficit in spatial orientation?

On the basis of studies of brain-injured war veterans, Semmes and Teuber (e.g. Semmes et al., 1963; Teuber, 1964) concluded that frontal lobe lesions produced a deficit in personal orientation and that this deficit was dissociable from a deficit in extrapersonal orientation that was characteristic of patients with more posterior lesions. This idea proved extremely influential and there have been claims of a parallel distinction in nonhumans as well (e.g. Pohl, 1973). There are several reasons to doubt the validity of this proposition, however.

First, the deficit on the "personal orientation test" is not necessarily purely spatial. The task requires that patients look at a series of drawings of a man, upon which there are several numbers on different points on the body, and to point to the same locations on their own body. On some of the drawings the back of the man is drawn, and for some of the drawings the front of the man is drawn. The correct solution of the task requires an understanding of the spatial location of the points but it also requires that the patients keep changing the correct rule for solution since the front-sided drawings require a 180° rotation of the figure whereas the back-sided drawings do not. Furthermore, the numbers move all over the body so that the correct answer requires that the subject change the location for each response. As Teuber stated in 1964, "What is not clear is whether the repeated reversal (of a principle) per se produced the difficulty on this task for our frontals, or whether the main difficulty was more specifically related to orientation and reorientation of the body" (Teuber, 1964, p. 438). This question remains today. Second, although subsequent studies with human subjects have shown deficits on various tests requiring the use of spatial information, such as finger and stylus maze tests (Corkin, 1965; Milner, 1965), all of the latter tests confound space and memory. Third, in our own studies on rats with prefrontal lesions we were initially impressed with their deficits on various spatial maze learning tasks but these tasks all confound temporal memory with spatial information. That is, the animal must keep a neural record of both the route it followed to find the platform, as well as the location of various extra-maze cues to the platform location, in addition to being able to recognize the correct configuration of spatial elements that identify the spatial location of the platform. A deficit in either the neural record or in the synthesis of the spatial information would lead to poor performance. Further, on the Morris water task there is only an acquisition deficit, and not a retention deficit (e.g. Sutherland, 1985). If the prefrontal cortex had a significant role in spatial orientation per se, one would expect a deficit on both acquisition and retention of spatial problems. In addition, it is clear that frontal lobe patients are not impaired at most tests of spatial rotation or spatial manipulation (DeRenzi, 1982), again suggesting that there may not be a unique spatial function of the prefrontal cortex. In summary, although frontal lesions impair the performance on tests of spatial orientation and/or navigation, there is no compelling evidence of a unique spatial function of the prefrontal cortex.

Is there a general class-common function of the frontal lobe?

There have been repeated attempts to develop theories of the general role of the prefrontal cortex in the control of behaviour, and although they vary in detail, there is a common theme over the last decade that the prefrontal cortex is involved in the temporal organization of behaviour (e.g. Fuster, 1980; Goldman-Rakic, 1987). The temporal control of movement requires at least 6 components. First, there must be an ongoing record of sensory stimulation that has occurred recently. This allows for behavioural responses to be discontiguous with sensory stimulation. This capacity is taxed in delay-type tasks. Second, there must be an ongoing record of what movements are being produced by the "motor system" at any given moment. It is only with this knowledge that new units

or series of units can be initiated. Third, there must be a record of those behaviours that are already executed. This is especially important in situations in which appropriate behaviours are contingent upon previous behaviours, such as in chains of movements. Moreover, a record of past behaviours is needed for strategies of searching since we must keep track of where we have searched. Fourth, there must be inhibition of some motor impulses and excitation of others in order to produce appropriate behavioural sequences. For example, in order to type we need to inhibit certain finger movements and activate others, and of course to do so in the correct order. Fifth, behaviour must be flexible with respect to both internal and external environments. It is one of the characteristics of mammals that we are able to adapt behavioural patterns to changing contexts. The importance of context-dependent behaviour in primate social structure is beautifully illustrated in Jane Goodall's graphic descriptions of the different behavioural patterns exhibited by chimpanzees (Goodall, 1986). Thus, the make-up of the social group at any time dictates the behaviour of each chimpanzee. Given the presence and position of certain animals a given chimp may be bold and relaxed whereas within a different mixture of chimps they are quiet and nervous. Further, it appears that an error in evaluating the context can have grievous consequences. It may be no accident that the frontal lobe has grown so large in primates who are so highly social. Not only must behaviour be regulated by external context but also by internal context, such as autonomic and endocrine status. This presumably accounts for the close relationship between the prefrontal cortex and autonomic systems (see Neafsey, this volume). Sixth, there must be an ongoing monitoring of the consequences of behaviour. If reward is associated with a particular series of movements, but not with another, then the association between movements and consequences needs to be made.

I have argued elsewhere (Kolb, 1984) that whereas the principle of temporal organization of behaviour provides a basis for the unity of prefrontal function, the necessary components for such a function provide the basis for the diversity in the effects of frontal injury. In the absence of an ongoing record of stimulation and behavioural responses, behaviour will appear disorganized. This may be clearly seen in the disruption of various species-typical behaviours such as mating behaviour, maternal behaviour or nest building in rats with prefrontal lesions. The prefrontal cortex is essential for the eventual execution of most of these behaviours (e.g. Whishaw, 1990) but in the absence of prefrontal cortex the complete behavioural action patterns are seldom executed correctly. Furthermore, in the absence of temporal memory, behaviour becomes dependent upon the environmental cues that are present when behaviour is executed. That is, behaviour will not be under the control of internalized knowledge, but of external cues that are present. This may manifest itself in any number of ways, one of which is likely to be a loss of internal inhibition of behaviour.

Conclusion

One of the characteristics of the mammalian cortex is that the sensory systems have evolved multiple representations in each sensory modality. It appears that as this evolution of sensory cortex has occurred there has been a corresponding increase in the volume of prefrontal cortex with which the sensory areas are associated (Fig. 4). It seems likely, therefore, that the prefrontal cortex will have multiple systems designed to provide temporal organization of behaviours related to different types of sensory inputs. It is clear from studies of nonhuman primates that lesions in different prefrontal loci will produce deficits in different delay tasks, each of which may require different types of information (e.g. Mishkin and Appenzeller, 1987; Passingham, 1985). One key to understanding the details of prefrontal organization in mammals may therefore be found in the study of both the cortico-cortical inputs to different prefrontal areas as well as in the study of the

differences in behavioural patterns of different mammalian species. These behavioural patterns have evolved in response to specific ecological pressures and the unique pattern of cortical development in different species will likely reflect the different neural requirements for particular species-typical behaviours. The apparent general similarity in prefrontal function across mammals may reflect the general requirements of temporally organizing behaviours in animals with behavioural repertoires that are far more plastic than those of other classes such as birds or reptiles. The interspecies differences in the details of prefrontal organization may reflect the differences in sophistication of the temporal organization of behaviour, or at least of certain classes of behaviours.

As Warren (1972) has pointed out, neuropsychologists have concentrated upon the search for general principles regarding the neural mechanisms of behaviour and have tended to ignore interspecies variability, and the adaptedness of behaviour. It has been the goal of this paper to show that there are general similarities in prefrontal function and organization. I believe, however, that neuropsychologists also can effectively study prefrontal function by taking advantage of the differences in behaviour and prefrontal structure in different mammals, and that this will provide a complementary approach to unravelling prefrontal function. Thus, animal models have provided evidence of unity of prefrontal function in mammals and offer promise of providing evidence of the diversity of prefrontal function as well.

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Discussion

J.P.C. de Bruin: The Masterton and Skeen data show a correlation between size of PFC and delay interval which can be "mastered". You presented in one of your studies the opposum, what about other marsupials like Echidna (cf. Divac et al.). Would its large PFC predict a good performance in tests with a long delay interval?

B. Kolb: This is difficult to know since there are no functional data on the Echidna but the prediction is straightforward: they should be good on tests like delayed alternation. Curiously, however, cats have a rather modest PFC, yet at least wild cats are rather good at delays.

A.Y. Deutch: The social behavior of the lab rat is very "truncated" relative to the social organization of the wild rat. Should we study the *lab* rat, or look as well to wild rats?

B. Kolb: The data from various labs are quite clear on the natural behaviour of the lab rat: it is not qualitatively different from the wild rat, although there are quantitative differences. I thus see no problem with studying lab rats. It would be interesting, however, to see if there is a difference in the size, or dendritic structure, of the PFC in wild rats since there are interspecies differences in social structure and volume of PFC in different species of voles.