Introduction

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INTRODUCTION

One of the major debates in studies of the prefrontal cortex has been whether this cortical region should be considered to have unitary or heterogeneous functions. In the past, progress in addressing this issue has been hampered by an inadequacy in our understanding of the complex cognitive and emotional processes that may be subserved by this region of the brain. Whilst poor judgement, planning and decision making were recognizable characteristics of damage to the prefrontal cortex, the component psychological processes that contributed to these complex cognitive capacities were poorly understood, making it difficult to characterize the precise role of the prefrontal cortex in the expression of these functions. Moreover, the commonly used, but ill-defined terms of 'executive processing' and higher-order cognitive processing', used to describe the overall function of the prefrontal cortex, have only added to the confusion.

From the early ablation studies in monkeys two cognitive processes emerged that appeared to be dependent upon an intact prefrontal cortex, 'short term memory', as measured primarily by performance on the delayed response paradigm and 'behavioural inhibition', as measured by performance on discrimination reversal and go/no go paradigms. Deficits in these processes became associated with damage to the dorsal and ventral regions of the prefrontal cortex, respectively (Mishkin 1964; Iversen & Mishkin 1970; Fuster 1980). However, on closer examination, the anatomical differentiation of these two processes within the prefrontal cortex was far from clear. For example, Diamond & Goldman-Rakic (1989) identified disinhibitory components to the impaired performance of monkeys with lesions of the dorsolateral prefrontal cortex on the spatial delayed response task. Conversely, lesions of the inferior prefrontal convexity, commonly associated with perseverative responding on a visual discrimination reversal task (Iversen & Mishkin 1970), subsequently were shown to impair an object version of the delayed response task (Kowalska *et al.* 1991). Thus, from ablation studies in monkeys it was proving difficult to identify a set of general principles that could account for all the experimental findings and which would thereby characterize the overall functional organization within the primate prefrontal cortex.

In parallel with the studies in monkeys, functional differences between the dorsal and ventral surfaces of the prefrontal cortex also emerged from investigations in humans although in contrast to monkeys, the distinction was between cognitive and social/emotional aspects of behaviour rather than between short term memory and behavioural inhibition. However, while deficits in cognitive tasks following dorsolateral prefrontal lesions in humans were easily captured in the laboratory in a large range of tests, including tests of planning, such as the Tower of London (Shallice 1982), and tests of cognitive flexibility such as the Wisconsin card sorting test (WCST) (Milner 1963, 1982), it proved harder to capture the deficits in patients with ventral frontal damage in the laboratory even though these patients had profound social and emotional abnormalities and were severely disrupted in their everyday activities. This highlights one of the discrepancies between studies of prefrontal function in monkeys and humans since in monkeys, unlike humans, it has been relatively easy to obtain deficits in performance of standard laboratory tests following damage to ventral regions of prefrontal cortex (see above). Another discrepancy between monkey and human studies has been that cognitive inflexibility (or behavioural disinhibition) is associated with damage to dorsolateral regions of prefrontal cortex in humans, as shown for example, by impaired performance on the WCST (Milner 1963), while perseverative deficits in monkeys are associated primarily with damage to ventral regions of the prefrontal cortex (Mishkin 1964; Iversen & Mishkin 1970).

Such inconsistencies both within species, as well as between species, regarding the functional organization of the prefrontal cortex, along with a paucity in our knowledge of the complex psychological processes subserved by this region, have begun to be addressed over the last few years, with new theoretical, as well as technical, advances. It was these issues that were the focus of the Discussion Meeting held at the Royal Society. One obvious advance has been in our understanding of the anatomical organization of the prefrontal cortex, particularly with respect to the non-human primate brain, a topic that is taken up by the paper of Pandya & Yeterian. A far greater number of regions within the prefrontal cortex are recognized today than as little as ten years ago, based largely upon studies of cyto- and myeloarchitecture (Preuss & Goldman-Rakic 1991; Carmichael & Price 1994; Petrides & Pandya 1994) and patterns of connectivity (Carmichael & Price 1995*a,b*) within the frontal lobes of the Macaque. Since the majority of ablation studies in monkeys have been based upon the subdivisions proposed by Walker (1940) it is evident that in many of these studies the lesions, inadvertently, extended across a number of different subdivisions of prefrontal cortex. Therefore, with hindsight, this may have contributed to the difficulty in identifying functional distinctions between the various regions of prefrontal cortex in the monkey. In addition, discrepancies between functional studies in monkeys and humans may, in part, have been due to an inadequate understanding of the comparable regions of prefrontal cortex in monkeys and humans. However, this too has been addressed recently by a comparative study of the neural architecture of the prefrontal cortex in humans and monkeys by Petrides & Pandya (1994) which will provide us with a far better framework for relating experimental studies in monkeys and humans.

The ability to extrapolate findings in monkeys to humans has also been improved by another major advance in prefrontal research, namely the use of comparable tests of cognition in human and non-human primates, an approach that was illustrated in several of the papers presented at this Discussion including those of Petrides and Robbins. Such an approach, the merits of which were first realized in the study of human memory and vision (Weiskrantz 1977), is now being used in all fields of cognitive brain research as the identification of common brain regions subserving superficially similar behavioural functions strengthens the likelihood that the same cognitive functions are being studied in both species (Roberts 1996). Notably, it has been used successfully to advance our understanding of the neural basis of memory (Squire *et al.* 1988; Gaffan 1991; Gaffan *et al.* 1991) and visuo-spatial attention (Petersen *et al.* 1987; Posner *et al.* 1988), to identify the neural and neurochemical basis of a variety of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease (Flicker *et al.* 1984; Morris *et al.* 1987; Freedman & Oscar-Berman 1989), and neuropsychiatric disorders such as schizophrenia (Frith & Done 1983; Ridley *et al.* 1988). With respect to the study of the prefrontal cortex, Milner & Petrides have taken various frontal lobe tests classically used in monkeys and adapted them for use in humans, including their self-ordered pointing task (Petrides & Milner 1982) (which was adopted from the internal and external generated sequencing tasks used to study frontal lobe function in monkeys by Brody & Pribram (1978)) and the visual conditional associative learning tasks (Petrides 1985). Similarly, Freedman & Oscar-Berman (1986) and Verin *et al.* (1993) have tested patients on the spatial delayed response and alternation tasks as well as visual discrimination tasks. Whilst originally, these tests were considered to be too 'easy' for humans and therefore unlikely to be sensitive to frontal lobe damage in humans this has been shown not always to be the case. Patients with frontal lobe damage can be impaired on these delayed response tasks and the saccade-response version of the spatial delayed response task, devised by Goldman-Rakic (1995), is now used successfully in functional neuro-imaging studies (Jonides *et al.* 1993). In addition, a recent study by Rolls *et al.* (1994) has reported deficits on reversal of a go/no go task in patients with damage restricted to the orbitofrontal cortex. Not only is this latter finding consistent with the original studies in monkeys demonstrating reversal deficits following damage to the orbitofrontal cortex but it demonstrates, in addition, that it is possible to find impairments following orbitofrontal damage in humans using standard laboratory tests.

Moving in the opposite direction, Roberts *et al.* (1988) have adapted a clinical test of frontal lobe function, for use in monkeys, namely the Wisconsin card sorting test (WCST).

Using this paradigm it has been shown that the deficits in frontal patients shifting an attentional set from one perceptual dimension to another, such as shifting from colour to shape, as required in the WCST, are probably the result of damage to a different region of prefrontal cortex to the perseverative deficits seen in monkeys on the visual discrimination reversal task which requires monkeys to shift responding from one specific visual stimulus to another (Dias *et al.* 1996). These findings not only raise the possibility that 'response inhibition' may be a general process carried out by a number of different regions of prefrontal cortex but also that different regions of prefrontal cortex are involved in different aspects of cognitive processing even within the same modality. In this example, the attentional processing of visual patterns is carried out in an area distinct from that involved in the 'affective' processing of visual patterns.

Of course, this organization must be integrated with another level of organization within the prefrontal cortex based upon sensory-specific domains that has been proposed by Wilson *et al.* (1993) from their electrophysiological recording studies. This leads us onto a third major advance in the field of prefrontal research which has been in our understanding of the relationship between neuronal activity within the prefrontal cortex and ongoing behaviour. In humans this has been at the 'macro-level' of analysis, studying event-related potentials over the scalp, in intact as well as frontal lesioned patients. This work has identified, for example, the importance of the prefrontal cortex in 'inhibition' and 'novelty detection' (Knight 1991). In monkeys, such analysis can be performed at the cellular level and has been used successfully to study the role of the prefrontal cortex in mnemonic (Goldman-Rakic 1995) and associative (Thorpe *et al.* 1985) processes, issues that will be considered in detail in the papers by Goldman-Rakic and Rolls. Together, this approach is providing insight into the neuronal operations that are performed by the prefrontal cortex, an important step towards an understanding of the component cognitive mechanisms that contribute to higher-order executive processing.

A fourth major advance has come with the use of functional neuroimaging which is providing further insight into the functional organization of the prefrontal cortex in humans. For example, a recent study by Courtney *et al.* (1996) has highlighted a dissociation between object and spatial working memory within ventrolateral and dorsolateral prefrontal cortex, respectively, in agreement with the findings of Wilson *et al.* (1993) in monkeys. This finding supports the hypothesis that one level of organization within the prefrontal cortex is based upon sensory-specific processing. Yet another level of organization to have been identified with functional neuroimaging is hierarchical in nature and will be discussed in the paper of Petrides with respect to a two-stage model of working memory (Petrides 1994). In addition, this technique is also providing us with insight not only into the functional interactions between the prefrontal cortex and the rest of the brain including the basal ganglia (Goldberg *et al.* 1990), the processing modules of the posterior neocortex (Frith *et al.* 1991) and the non-specific arousal systems of the reticular formation (Daniel *et al.* 1991; Grasby *et al.* 1992; Dolan *et al.* 1995) but also between different regions, and thus potentially different processing modules, within the prefrontal cortex itself. Many of these are highlighted in the papers by Passingham, Weinberger and Frith. Of course, functional neuroimaging, using the 2-deoxyglucose method, can also be used to visualize the interactions of the prefrontal cortex with other brain areas in monkeys and has been used successfully by Friedman & Goldman-Rakic (1994) to identify those areas, in addition to the dorsolateral prefrontal cortex, that are involved in performance of the spatial delayed response task, including the parietal cortex.

Finally, major conceptual advances in human neuropsychology and cognitive psychology drawing upon artificial intelligence and connectionism, have contributed greatly to our understanding of executive functioning. These have brought to the fore the issues that have to be addressed when referring to 'executive' function and whether it is helpful or not to think of this as a 'unitary' system or as a 'multiple processing' system. Aspects such as these will be discussed in the papers of Baddeley & Della Sala, and by Shallice & Burgess. In attempting to fractionate 'executive' functioning into several distinct component processes Shallice & Burgess (1991) have developed a concept of 'markers' which act to interrupt ongoing behaviour and trigger new plans of action, if appropriate. They have suggested that this 'marker' process may be particularly impaired in patients with orbitofrontal damage and may explain the profound organizational deficits apparent in the daily activities of such patients. This concept of markers, has also been introduced, independently, by Damasio in his 'somatic marker hypothesis' which focuses on the role of emotional processing in the orbitofrontal cortex in the control of complex decision making (Damasio *et al.* 1991). Whether these different, but perhaps related concepts of 'markers' can be integrated into an overall model of prefrontal function remains to be determined. Interestingly, Damasio proposes that possible neural substrates of his somatic markers may include the non-specific arousal pathways that innervate the prefrontal cortex, including the monoaminergic and cholinergic systems. Few studies have investigated the role of these systems specifically with respect to the modulation of prefrontal function and even fewer have assessed their possible differential contribution to prefrontal function (Brozowski *et al.* 1979; Sawaguchi *et al.* 1990; Sawaguchi & Goldman-Rakic 1991; Roberts *et al.* 1992, 1994). However, the role of one of these, dopamine, will be considered at the cellular level in the paper by Goldman-Rakic and at the behavioural level in the papers of Robbins and Diamond, the latter drawing upon evidence from her studies on PKU deficiency in children. The role of dopamine will be taken up again in the final paper by Cohen, which, drawing upon neurobiological as well as psychological evidence, will illustrate the use of computational models in making explicit the mechanisms within prefrontal cortex that may underlie executive processing.

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