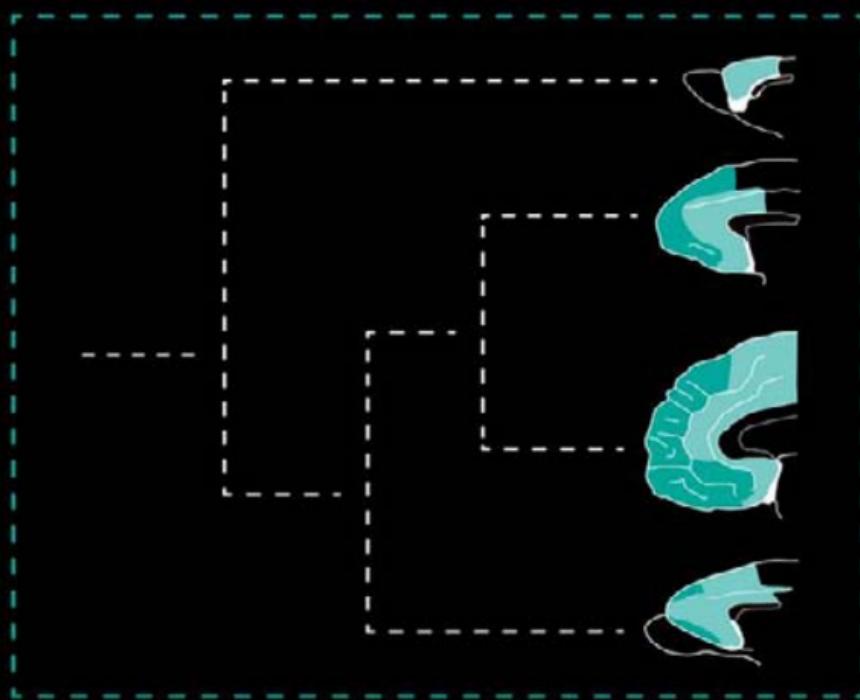


THE NEUROBIOLOGY OF THE PREFRONTAL CORTEX

ANATOMY, EVOLUTION, AND
THE ORIGIN OF INSIGHT

Richard E. Passingham and Steven P. Wise



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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
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First Edition published in 2012

Impression: 1

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British Library Cataloguing in Publication Data

Data available

Library of Congress Cataloging in Publication Data

Library of Congress Control Number: 2012935803

ISBN 978–0–19–955291–7

Printed and bound by
CPI Group (UK) Ltd, Croydon, CR0 4YY

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Dedication

In memory of

Patricia S. Goldman-Rakic (1937–2003)

Edward V. Evarts (1926–1985)

Edward G. Jones (1939–2011)

Animals studied by Americans rush about frantically, with an incredible display of hustle and pep, and at last achieve the desired result by chance. Animals observed by Germans sit still and think and at last evolve the solution out of their inner consciousness.

—Bertrand Russell, *An Outline of Philosophy* (1925)

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Preface

In the 1960s, the Russian neuropsychologist Alexander Luria gave a much anticipated lecture in London, which one of us attended. He started by drawing a brain on the blackboard and placing a large question mark over the prefrontal cortex. At the end of the lecture, he triumphantly rubbed out the question mark. Readers of this book will not be so lucky.

Why prefrontal, why now?

One of us had a go in an earlier book, *The Frontal Lobes and Voluntary Action* (Passingham 1993). That book treated the frontal lobes as a whole, including its motor areas, and it suggested that their key functions involve conditional behaviour. In this kind of behaviour, one sensory context determines which action to take and other contexts lead to other actions.

The publisher later asked for a second edition, but a simple revision was out of the question. Too much has changed. The 1993 book appeared in the infancy of functional imaging, which has altered the field profoundly. The book proudly showed a brain scan as the frontispiece and described the first author's early results from positron emission tomography—and that was all. The intervening years have seen thousands of imaging papers, with more on the prefrontal cortex than on anything else.

Two other major advances have also changed the field. First, neuropsychological studies in monkeys have experienced a renaissance. Recent studies differ from earlier ones in their use of more sophisticated experimental designs, which often focus on advanced cognition. Second, neurophysiological studies in monkeys have matured considerably, and for similar reasons. Neurophysiologists can now address the advanced cognitive capacities that epitomize primate behaviour. They do so with a broader array of tasks, and better control conditions, than anyone imagined in 1993.

So what follows is a new and different book, and not a second edition. We decided to write it because we have retired from laboratory research. One of us doesn't like gardening, and the other tends a very small one. We decided to write the book together because both of us have thought and written about the prefrontal cortex for some time now, and neither of us believes that our previous contributions provide a satisfactory solution to the problem.

A comparative approach

As readers might gather from what we have said so far, this book relies heavily on monkey research. But this does not mean that we ignore advances that have come from imaging in healthy people or from studies of patients. Indeed, we make extensive use of them. But in doing so, we interpret these advances in the light of the knowledge gained by studying other primates.

We recognize that many neuroscientists proceed without using this knowledge and that they do so very successfully. Cognitive psychologists do not, as a rule, concern themselves with the details of research on monkeys, and they have advanced our knowledge considerably. Likewise, the bulk of imaging research makes little use of what we know about other primates, and the field continues to prosper. However, it seems to us that in using imaging to explore the vast array of human abilities, one may fail to appreciate a simple fundamental function that ties everything together. The comparative perspective that comes from studying other primates can help us see the big picture.

Our comparative approach also explains the title of this book. We place what we know about the prefrontal cortex in an evolutionary perspective. This seems to us to be more like neurobiology than like standard neuroscience or neuropsychology. And so we call the book *The Neurobiology of the Prefrontal Cortex*.

The epigraph of this book reflects our comparative slant, as well (p. v). Russell (1925) was contrasting the studies of rats and cats by American psychologists such as Thorndike (1898) with the studies of chimpanzees by Germans such as Köhler (1925). Thorndike stressed a general-purpose, reinforcement mechanism for learning by trial-and-error. The trouble with trial-and-error learning is that it is resigned to many errors, and especially so in unusual circumstances. In this book, we claim that primates do not come to each new situation afresh. Instead, they swiftly and extensively transfer what they have learned to novel and rare situations. This is the insight of which Kohler wrote, and we believe that it depends upon the prefrontal cortex.

Style and terminology

We have chosen a style that contrasts with a typical academic monograph in several ways. This book makes no effort to achieve comprehensive coverage or to recount the history of the field. Several thousand papers are published on the prefrontal cortex each year. We could not write, and no reader could tolerate, a comprehensive review. So we engage unapologetically in cherry-picking evidence to advocate a position. We realize the danger of this approach: one can easily ignore contrary evidence and so create the illusion of clarity where none exists. But we find it preferable to an exhaustive review that leaves readers exhausted—but none the wiser.

Everyone seems to have their own language for discussing the prefrontal cortex. So some brief notes about terminology might prove helpful:

- ◆ We use some convenient but loose terms. When we use the word animals we mean nonhuman animals, and by monkeys we mean macaque monkeys, unless otherwise stated. We also know that some people object to the phrase great ape, but we suspect that readers will know what it means. We mean no disrespect to lesser apes, which we hold in high esteem.
- ◆ We use the anatomical terms caudal and posterior interchangeably. These terms are not, strictly speaking, synonymous, especially in humans, but they are close enough for our purposes. Likewise for rostral and anterior. We also adopt the phrase *granular prefrontal cortex*, although we know that its anatomy is not truly granular, as the primary sensory areas are.

- ◆ Much of the book relates results from experimental lesions. For convenience, we use the term *lesion* to cover all kinds of procedures that prevent a cortical area from functioning normally. These techniques include surgical removal, cell death due to excitotoxic agents, inactivation with inhibitory transmitters or cooling, optogenetic methods, and disruption of function by magnetic or electrical stimulation.
- ◆ In another convention, we use the term *activity* to describe the rate of neuronal action potentials, commonly known as firing, discharge, modulation, or spiking, but we use the term *activation* to describe results from imaging experiments, mainly from functional magnetic resonance imaging (fMRI). Chapter 1 explains why.
- ◆ We use the term *imaging* when the context makes it clear that the study measures activations, usually with fMRI, as opposed to structural imaging.
- ◆ We use several abbreviations, which are listed after the acknowledgements. Where we think that the reader might need reminding of the unabbreviated form, we spell it out again from time to time.
- ◆ The glossary explains selected terms from psychology and biology.
- ◆ After the preface, we use the abbreviation PF for prefrontal cortex throughout the book.
- ◆ When we refer to regions within the prefrontal cortex, we usually do so by placing the regional name before PF, as in *orbital PF cortex*. Occasionally, when the regional descriptors get too long, we shorten them or use other abbreviations, such as OFC for the orbital frontal cortex.
- ◆ Finally, like many people of our age, we persist in using the word *subjects* rather than participants to describe people who take part in experiments. It seems to us that only editors object to this, not the subjects themselves. We hope that no one feels subjugated as a result.

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Acknowledgements

We have many people to thank, and the book's dedication reflects three of these debts. When the first author wrote his Ph.D. thesis in 1971, Pat Goldman, as she then was, asked for a copy, and her continued support meant more than she ever knew. Without the guidance of Ed Evarts and Ted Jones, the second author would know next to nothing about neurophysiology or neuroanatomy. We dedicate this book to their memory.

We also acknowledge the privilege, early in our careers, of indulging our interest even when the heads of our laboratories did research on different topics. Our mentors allowed us free range: George Ettlinger, Alan Cowey, and Larry Weiskrantz for the first author; Ed Evarts and Ted Jones for the second. We appreciated it immensely.

Two of our many collaborators stand out. In 1988, the first author heard a talk in Oxford by Richard Frackowiak in which he described some early imaging experiments. A series of collaborative studies followed at the Hammersmith Hospital. To continue his imaging studies, the first author later moved with Richard to the Functional Imaging Laboratory, later to become the Wellcome Centre for NeuroImaging. It is one of Richard's most impressive achievements that he created and ran this laboratory.

The second author went decades between collaborations with Betsy Murray, but when they resumed, the results changed his view of the prefrontal cortex forever. Both her own lines of investigation and their collaborative research produced findings that led to some of the key ideas in this book.

We appreciate the help of several colleagues who commented on drafts of various chapters: Mark Baxter, Mark Buckley, Silvia Bunge, John Duncan, Hakwan Lau, Monica Muñoz, Betsy Murray, Todd Preuss, Matthew Rushworth, Katz Sakai, Chris Summerfield, Jun Tanji, Satoshi Tsujimoto, and Mark Walton.

We also thank our editors at Oxford University Press, Charlotte Green and Martin Baum, for their encouragement. Anita Butterworth provided welcomed assistance with the figures.

Over the years, graduate students and postdoctoral fellows have contributed more and more to our ideas. One gets set in one's ways and so need to have younger people around. Our ideas on the prefrontal cortex have been particularly stimulated by Sara Bengtsson, Driss Boussaoud, Peter Brasted, Tim Bussey, Tony Canavan, Marie-Pierre Deiber, Giuseppe di Pellegrino, Aldo Genovesio, Harri Jenkins, Louise Johns, Markus Jueptner, Hakwan Lau, Misha Lebedev, Sohie Lee, Narender Ramnani, James Rowe, Matthew Rushworth, Katz Sakai, David Thaler, Ivan Toni, Satoshi Tsujimoto, and Ilsun White.

As this list shows, one of the privileges of science is that it is an international community. In addition to young scientists from Britain and the United States, we have worked with others from Australia, Brazil, Canada, China, France, Germany, Hong Kong, Italy, Japan, Russia, Sweden, and Taiwan. It keeps the mind alive, and it is what we miss most in retirement.

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List of abbreviations

~	approximately	MIP	medial intraparietal cortex
AIP	anterior intraparietal cortex	MST	middle superior temporal area
BOLD	blood oxygen-level dependent [signal]	MT	middle temporal area
CMAr	rostral cingulate motor area	OFC	orbital frontal cortex
CMAs	cingulate motor areas	PET	positron emission tomography
DTI	diffusion tensor imaging	PF	prefrontal cortex
EEG	electroencephalography	preSMA	presupplementary motor area
FEF	frontal eye field	ROC	receiving operating characteristic
fMRI	functional magnetic resonance imaging	rTMS	repetitive transcranial magnetic stimulation
GrAD	antero-dorsal granular area	S1	primary somatosensory cortex
GrAL	antero-lateral granular area	S2	second somatosensory cortex
GrD	dorsal granular area	SEF	supplementary eye field
GrM	medial granular area	SEM	standard error of the mean
GrP	posterior granular area	SMA	supplementary motor area
GrPL	postero-lateral granular area	STP	superior temporal polysensory area
GrPM	postero-medial granular area	TE	part of the inferior temporal cortex
GrV	ventral granular area	TEO	caudal part of the inferior temporal cortex
Ka	thousand years ago	TMS	transcranial magnetic stimulation
LIP	lateral intraparietal cortex	TPO	polysensory superior temporal area
Ma	million years ago	WGTA	Wisconsin general testing apparatus
MD	mediodorsal nucleus of the thalamus		

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Glossary of terms from biology and psychology

Term	Usage and synonyms	Exclusions and antonyms
Advanced	Divergent from the ancestral condition	Does not imply greater complexity or sophistication
Analogy	Structures or behaviours in two or more species having a common function	
Anthropoids	A group of primates that includes all modern monkeys, apes, and humans, along with extinct descendants of the ancestral anthropoid	
Attention	The enhanced processing of a subset of available information, sensory or mnemonic	
Catarrhines	A group of primates that includes Old World monkeys, apes, and humans	
Choice	The selection of a goal or an action among alternatives	Differs from a decision
Conjunction	A combination of representational elements	
Current context	Sensory inputs and recent events	
Decision	Perceptions about the world	Differs from a choice and an action
Episodic memory	Recollection of events, implying awareness	
Event	One-time conjunction of contexts, goals, actions, and outcomes at a particular time and place	
External guidance	Behaviour based on external sensory inputs	Contrasts with 'internal'
Goal	An object or place that serves as the target of an action	Does not include rewards or outcomes
Habit	The result of overtraining, which produces a response to a stimulus without reference to a predicted outcome	In psychology, a habit is learned and does not include innate behaviour
Haplorhines	A group of primates that includes tarsiers and anthropoids	
Homology	A trait occurring in two or more species because of inheritance from a common ancestor	
'Internal' guidance	When no sensory input prompts behaviour	Contrasts with external
Memory	Stored information	
Need	Biological requirements such as food and fluid; synonyms: drive, motivation	

Outcome	Benefit or harm produced by a stimulus or behaviour	Not synonymous with goal
Prepotent response, behaviour	Innate, habitual, or conditioned response	
Primitive	Resembling the ancestral condition	Does not imply simplicity or a lack of sophistication
Prospection, prospective memory, prospective coding	Representation of a goal in short-term memory	Contrasts with retrospective memory, retrospective coding
Reinforcement	An outcome that serves as feedback	
Re-representation	Neural representations drawing on other, lower-order representations	Does not refer to activating a representation again
Response	An action that depends on conditioned associations with stimuli or outcomes	
Reward	A beneficial outcome	
Rule	A behavioural input–output algorithm	
Sign	A nonspatial cue that is less than a whole object but more than elemental sensory features	
Strategy	(1) One among two or more solutions to a problem; (2) a partial solution to a problem	
Value	Degree of cost or benefit	

^a In biology, the term habit often refers to innate traits. For example, many rodents have the fossorial habit of living underground, and many trees have the habit of growing tall.

Chapter 1

Introduction

Overview

This book presents a proposal on the fundamental function of the primate prefrontal cortex. In this chapter, we explain why we have adopted a comparative approach to the problem. We also explain why our proposal depends on understanding the connectional differences among cortical areas. Because we rely on findings from cell recordings, functional imaging, and brain lesions, this chapter explains how these methods relate to each other, taking into account their strengths and weaknesses. We stress several prerequisites for a successful theory of the primate prefrontal cortex: it must encompass a broad range of findings, it must say how the function of prefrontal cortex differs from that of other areas, it must explain the advantages that the prefrontal cortex brings, it must deal with the prefrontal cortex as a whole, and it must be testable.

Introduction

In this book we propose that the primate prefrontal (PF) cortex performs a simple fundamental function: it uses information about the current behavioural context to generate goals according to current biological needs, and it can do so on the basis of single events. That the PF cortex performs this function and how it does so are two of the principal topics in this book. We are well aware, of course, that many books and articles address these topics, but this book differs by addressing two additional ones as well: why the prefrontal cortex does what it does and how it got to be that way.

These issues arise because biology needs answers to two kinds of questions (Mayr 1982). Suppose that one asks why the heart rate accelerates in dangerous situations. One answer involves the physiological mechanisms that come into play when the brain detects danger and produces autonomic outputs, when smooth muscle contracts, and so on. The other answer concerns the evolutionary history that caused our brain, heart, and circulatory system to be as they are and to do what they do. Both physiology and phylogeny cause the heart to race.

Tinbergen (1951) elaborated on this concept by suggesting that we should ask four questions of any biological system: how did it evolve (phylogeny)?; how does it promote fitness (selection)?; how does it develop (ontogeny)?; and how does it work (mechanism)? Writings on the prefrontal cortex commonly tackle the last two questions, but they rarely

address the first two. Yet we believe that they hold the key to understanding the prefrontal cortex.

Of course, it is open to neuroscientists to say that they are not interested in evolution or fitness. But we think that they make a tactical mistake in doing so. As Chapter 2 explains, some parts of the PF cortex first appeared in early primates and others came along later in primate evolution. In ignoring this history, neuroscientists forfeit some important insights.

The fact is that we are anthropoid primates, a group of animals that descended from the last common ancestor of apes, humans, and monkeys. We see the world much like any other anthropoid, through a fovea that views the world in exquisite detail and, like most anthropoids, in full colour. Other kinds of mammals, and even other kinds of primates, lack these visual specializations. Compared to other mammals, we have an impoverished sense of smell and unremarkable abilities to taste and hear. But we learn about the world differently than these other mammals—and more effectively. The PF cortex provides the key to understanding not only how we do so, but also how this came about.

Aims

To achieve our ambitions, we set forth five aims, which state explicitly what we want to accomplish in this book. They are:

1. To say how the primate PF cortex evolved and what advantages it brings.
2. To say how its connections allow the PF cortex, but not other cortical areas, to perform its function.
3. To make a specific proposal concerning the fundamental function of the primate PF cortex.
4. To show how the proposed function accounts for imaging results acquired as people perform complex cognitive tasks.
5. To tell readers how our proposal differs from others in the literature and how to test it.

All of these aims are important. Consider what happens when we ignore the first one. To fulfil it, we need to understand the homologies among cortical areas in different mammalian species. Two popular ideas about the function of the PF cortex hold that its fundamental function is working memory (Goldman-Rakic 1998) or the monitoring of items in working memory (Petrides 1998). These functions have been attributed to a part of the PF cortex that, as Chapter 2 explains, evolved specifically in primates and which nonprimate mammals lack.

One might think that animals without homologues of this part of the PF cortex would lack working memory or the ability to monitor its contents. Yet the evidence is otherwise. Rats, for example, can learn the radial arm maze task. The experimenter baits each of the eight arms of the maze with a food pellet, and a hungry rat simply has to visit the arms once each in order to collect the pellets (Olton et al. 1982). The fact that rats can learn the radial arm maze task demonstrates that they can remember and monitor which arms they

have visited previously. So a comprehensive theory must explain why primates need certain parts of their PF cortex for tasks that other mammals can learn and perform without homologues of these areas.

Our second and third aims are especially important because they deal with the specific function of the PF cortex, as contrasted with the rest of the brain. If parts of the PF cortex evolved in primates, we need to understand what these areas can do that other parts of the brain cannot. The failure to do so undermines several theories. For example, the working memory (Baddeley & Della Sala 1998), global workspace (Dehaene et al. 1998), and multiple demand theories (Duncan 2010b) fail to distinguish between the roles of the PF cortex and the posterior parietal cortex. Both cortical regions are said to contribute to these functions. So these three theories ascribe to the PF cortex functions that other areas also perform. Yet, the key to understanding the primate PF cortex must lie in understanding how its function differs from that of other parts of the cortex.

Our fourth aim requires understanding how the simple function that we propose for the PF cortex accounts for activations that occur there while people perform complex cognitive tasks. There is such a wide variety of such tasks that a simple account seems hopeless. How, one might ask, could a *simple* function, however fundamental, account for activations during *complex* cognition?

Our fifth and final aim seems different from the others, but it is just as important. Many of the proposals in the literature are so general that they could never be refuted. Executive function, to take one example, has little to offer in the way of testable hypotheses. Is there any behaviour of significance that fails to involve executive function? Unlike some theories of the PF cortex, the idea that we advance should prove easy to refute: one merely has to show that some other part of the brain performs the function that we propose or that the primate PF cortex does not perform that function.

Our five aims determine the structure of this book. Chapter 2 addresses the first aim: exploring the evolution of the primate PF cortex. Chapters 3–7 take up the second aim, which is to say what its connections allow the primate PF cortex to do that other parts of the brain cannot do. The third aim deals with the function of the PF cortex as a whole, and so Chapter 8 advances the book's proposal. Chapter 9 addresses the fourth aim by examining the human brain-imaging literature. And Chapter 10 fulfils our fifth and final aim by comparing our proposal with other prominent ideas and suggesting how ours can be put to the test.

We hope that any neuroscientist who knows basic neuroanatomy can understand this book, but we do not assume any expertise on the PF cortex or the methods that are used to study it. Accordingly, the remainder of this chapter provides some background material on terms and some key methodological points.

Definitions and terminology

The PF cortex defined

Even experts sometimes use the phrase *frontal lobe* loosely. When Teuber (1964) considered the 'riddle of frontal lobe function', he meant the prefrontal cortex, not the frontal

lobe as a whole. In the discussion that followed a presentation by Aring and Fulton (1936), the neurologist Stanley Cobb lodged the following protest:

May I speak about nomenclature? This is thoroughly mixed up. The misunderstandings are largely due to a lack of precise use of terms. As I have listened here to the authors and discussants, I have heard ... them say [that the] frontal lobe was removed when they meant that the anterior two thirds of it was removed. I have heard motor area used to mean three different things and premotor area and pyramidal tract used equally loosely This colloquial talk may be genial, but it is not scientific!

We take these strictures to heart, and so we distinguish the PF cortex from the motor areas of the frontal lobe. We only use the phrase *frontal lobe* when we mean the whole of it or when we refer to lesions of the PF cortex that might have invaded or undercut the premotor areas.

We also make much of the distinction between granular and agranular parts of the prefrontal cortex. The cerebral cortex comes in types that can be categorized according to the number and density of cell bodies in the internal granular layer, layer 4. Granular areas have a conspicuous layer 4; agranular areas have fewer cell bodies condensed into a layer 4. This is an oversimplification, of course, but a useful one. The largest part of the primate PF cortex has a granular cytoarchitecture, and so many people call it the *granular prefrontal cortex* (Warren & Akert 1964).

Although this book focuses on the granular PF cortex, we include certain agranular areas within the PF cortex, as we define it. In chapters on the orbital and medial PF cortex we discuss both their granular and agranular parts. In doing so, we suggest the advantage that the granular parts of both regions confer upon primates.

Table 1.1 provides a list of the areas that we include in the PF cortex, and Table 1.2 presents groups of frontal areas. A list of the abbreviations that are used in the book and a glossary appear on p. xix and p. xxi, respectively. A bookmark placed at these pages might prove useful.

The PF cortex labelled

In order to discuss the primate PF cortex, we need to adopt a naming convention. As illustrated in Figure 1.1, von Bonin and Bailey (1947) called much of the granular PF cortex by a single name: area FD. That will not do for our purposes. Nevertheless, we present their map to show that the granular PF cortex has sufficient homogeneity that von Bonin and Bailey saw most of it as a single area.

In von Bonin and Bailey's nomenclature, the first letter of an area's name refers to a lobe: F for frontal, P for parietal, T for temporal, O for occipital, and L for limbic. The last letter designates an area within that lobe; for example, area FA means frontal area A as distinct from frontal area B.

Brodmann (1909) simply numbered his areas sequentially from the top of the brain to the bottom, as he encountered them in a series of horizontal brain sections. So area 4 is simply the fourth area from the top of the brain. Sometimes it is easy to relate the two nomenclatures; for example, area FA corresponds fairly closely to area 4. But sometimes von Bonin and Bailey saw the brain very differently from Brodmann.

Table 1.1 Prefrontal (PF) areas in human and macaque monkey brains. Area numbers in parentheses

Type	Area	Humans	Monkeys
Granular PF cortex	Caudal PF	Caudal lateral (8)	Precuate (8)
	Dorsomedial PF	Superior frontal gyrus and medial PF (9)	Superior frontal gyrus and medial PF (9)
	Lateral area 9	Superior frontal gyrus (9)	Superior frontal gyrus (9)
	Mid-lateral PF	Middle frontal gyrus (46)	Principal sulcus (46)
	Postero-lateral PF	Caudal middle frontal gyrus (9/46)	Caudal principal sulcus (9/46)
	Ventral PF	Inferior frontal gyrus (45, 47)	Inferior convexity (45, 12)
Agranular PF cortex	Granular orbital PF	Orbital surface (11, rostral 13, rostral 14)	Orbital surface (11, rostral 13, rostral 14)
	Polar PF	Frontal pole (10)	Frontal pole (10)
	Medial agranular PF	Anterior cingulate (24), infralimbic (25), prelimbic (32)	Anterior cingulate (24), infralimbic (25), prelimbic (32)
	Lateral agranular PF	Caudal areas 13 and 14 and agranular insular cortex	Caudal areas 13 and 14 and agranular insular cortex

Table 1.2 Terms for groups of frontal areas

Region	Components
Caudal PF	Area 8, including frontal eye field (FEF),?postero-lateral PF (area 9/46)?
Dorsal PF	Mid-lateral PF (area 46), lateral area 9,?postero-lateral PF (area 9/46)?
Medial PF	Infralimbic (area 25), prelimbic (area 32), anterior cingulate (area 24), medial area 9, and polar PF (area 10) ^a
Orbital PF, OFC	Granular & agranular orbital cortex (11, 13, 14), agranular insular cortex
Ventral PF	Area 12/47 and area 45,? area 44?
Lateral premotor	Dorsal and ventral premotor areas
Medial premotor	Presupplementary motor area (preSMA), supplementary motor area (SMA), cingulate motor areas (CMAs)
Premotor cortex	Lateral and medial premotor areas

^a Medial parts of the polar PF cortex in humans.

? An area that might be included in a group.

Nowadays, it is common to combine these two naming systems as seems most useful for some purpose. And a ‘Brodmann area’ no longer needs to correspond to anything that Brodmann himself described—or even imagined.

In addition to the granular and agranular areas of the PF cortex, Brodmann, von Bonin and Bailey, and many others have recognized intermediate types of cortex. Unlike agranular areas, which lack or nearly lack layer 4, and granular areas, which have a conspicuous

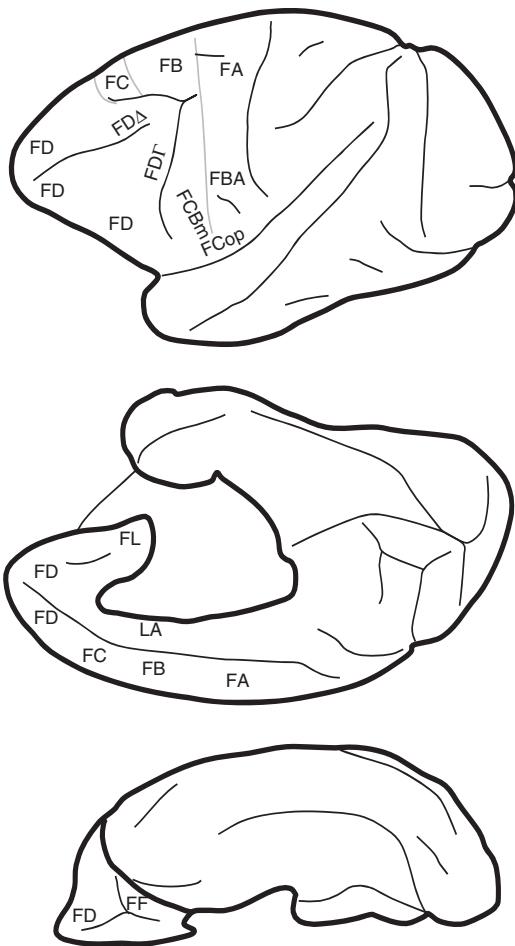


Fig. 1.1 Map of the macaque monkey cortex by von Bonin and Bailey (1947). Rostral is to the left, with a lateral view at the top (dorsal up), a medial view in the middle (ventral up), and a ventral view at the bottom (lateral up). Note that von Bonin and Bailey designated most of the PF cortex as area FD, although they recognized two agranular areas: FF and FL. Adapted from von Bonin G, Bailey P. *The Neocortex of Macaca Mulatta*, © 1947, University of Illinois Press.

layer 4, other areas have a dysgranular cytoarchitecture. This type of cortex has a thin and sometimes discontinuous internal granular layer. Von Bonin and Bailey's area FC has this property. And some areas, such as FCBm (Figure 1.1), have yet more intermediate properties, as designated by the combination of letters. As we said earlier, the distinction between granular and agranular PF cortex represents a useful simplification, not a rigid dichotomy. Mackey and Petrides (2010) used quantitative analysis to confirm that layer 4 becomes thicker and more conspicuous as one moves rostrally along the medial or orbital surfaces of the PF cortex.

In this book, we use an eclectic combination of names. For example, we use the letters TE and TEO for the inferior temporal cortex, as introduced by von Bonin and Bailey. We use the label area 6 for the premotor cortex, as used by Brodmann. And we use a hodgepodge of variants, for example, area 10 for the polar PF cortex, following Walker (1940).

The PF cortex divided

There is little consensus about subdivisions of the PF cortex. As just mentioned, von Bonin and Bailey distinguished relatively few frontal areas, but other anatomists have recognized many more. For example, Petrides and Pandya (1999, 2007) generated an architectonic map of macaque brains (Figure 1.2) that modifies Walker's by recognizing more subdivisions of the PF cortex.

Petrides and Pandya (1995) also produced a map of the human cerebral cortex (Figure 1.3), which matches their monkey map closely. However, Carmichael and Price (1994) viewed the brain differently. They studied the orbital and medial surfaces of the monkey PF cortex and recognized many more subdivisions than did Petrides and Pandya, and Öngür et al. (2003) did the same for the human brain.

Neuroanatomists have published conflicting maps of PF cortex because they disagree over whether and where they detect a border. In several other parts of the cerebral cortex, neurophysiology has provided topographic maps to help define an area. In visual, auditory, and somatosensory areas, a map of receptive fields can often define an area and its boundaries. Neurophysiology provides no such assistance for the PF cortex. Likewise, connections have helped define cortical fields. But the power to do so usually goes back to the topographic maps.

That leaves architectonics, the art of recognizing areas by selected structural features. When those features depend on stained cell bodies, the practice is called *cytoarchitectonics*. When they depend on the pattern of myelinated fibres, the term *myeloarchitectonics* applies. Together, they are called *architectonics*. It is an inexact science, to say the least. In essence, architectonics is a very high-dimensional pattern-recognition skill that takes years to master. For that reason, an objective, reliable, and faster way of marking the borders has been the holy grail of cortical architectonics for decades.

Schleicher et al. (1999) have explored a method that they call 'observer independent'. By this they mean that a human observer does not detect the borders, a computer does. Cell density changes from the most superficial cortex (layer 1) to the deepest part (layer 6). Optical density measures this variation, which reflects differences in the types of cells and packing density in the different layers. By taking these measurements in strips along the cortex, statistical methods can detect significant changes that demarcate a border between distinct cortical fields. Thus there is hope that one day we will have a complete map of the macaque cortex based on observer-independent methods. But we do not have one yet.

Even if one could establish areal boundaries with precision and reliability, they might not correspond to functional subdivisions. For example, in the primary motor cortex—area 4 of Brodmann and area FA of von Bonin and Bailey—its medial and lateral parts differ in cytoarchitecture, with larger cell bodies in the medial part. But this property simply results from the fact that the medial motor cortex controls the leg, and it has large cell bodies because their axons project farther down the spinal cord. Here the cytoarchitectonic difference does not correspond to a functional distinction, other than one involving different parts of the body. If an anatomist found a similar difference within the

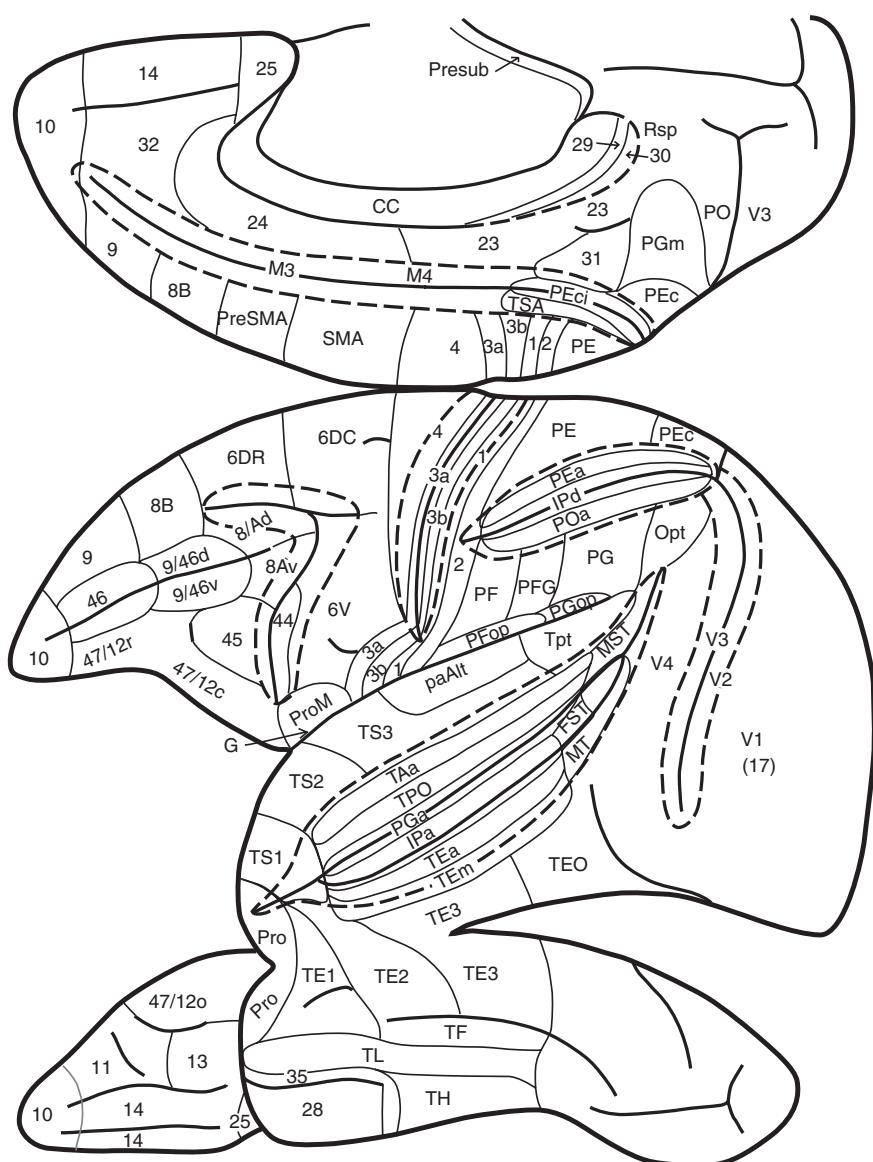


Fig. 1.2 Map of the macaque monkey cortex by Petrides and Pandya (2007). Rostral is to the left, with a medial view at the top (ventral up), a lateral view in the middle (dorsal up), and a ventral view at the bottom (lateral up). Abbreviations: CC, corpus callosum; G, gustatory cortex; Rsp, retrosplenial cortex; Pro, proisocortex, a variant of neocortex; PresMA, presupplementary motor area; SMA, supplementary motor area. Subdivisions of areas are often designated as dorsal (d or D), rostral (r or R), ventral (v or V), orbital (o), opercular (op), medial (m), caudal (c), or anterior (a). Reproduced from Petrides M, Pandya DN. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. *Journal of Neuroscience*, 27:11573–86, © 2007, Society for Neuroscience, with permission.

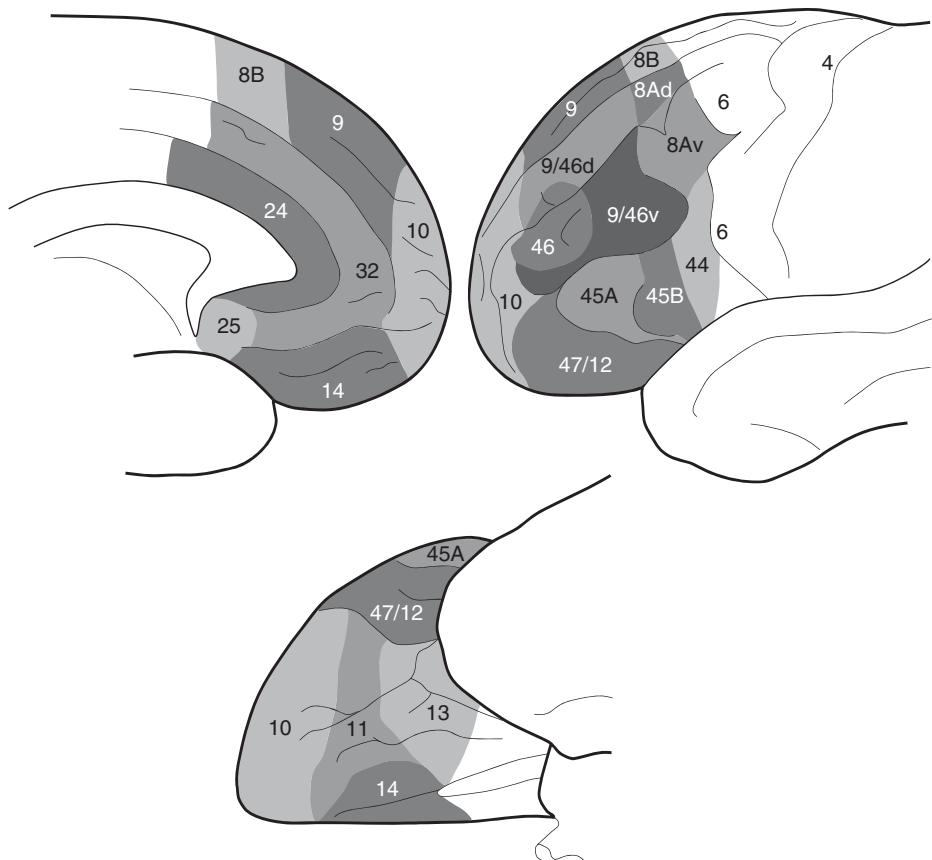


Fig. 1.3 Map of the human cortex by Petrides and Pandya (1999). In the medial view (top left), rostral is to the right; in the lateral view (top right), rostral is to the left; and in the ventral view (bottom), lateral is up. Adapted from Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience*, 11:1011–36, © 1999, John Wiley & Sons, with permission.

PF cortex, he or she would probably label the two zones as separate areas. But the distinction might indicate little or nothing about function.

In view of the problems and inconsistencies in identifying functional subdivisions of the PF cortex, we have opted to use general descriptive terms. Figure 1.4 shows these terms for the brains of macaque monkeys; Figure 1.5 shows their relation to sulci and numbered areas. This approach has the advantage of not being tied to any particular map, while remaining consistent with most of them.

Conventions and abbreviations

Our proposal depends critically on the connectional anatomy of the PF cortex. Accordingly, when we review results from imaging studies, we sometimes check where the peaks of

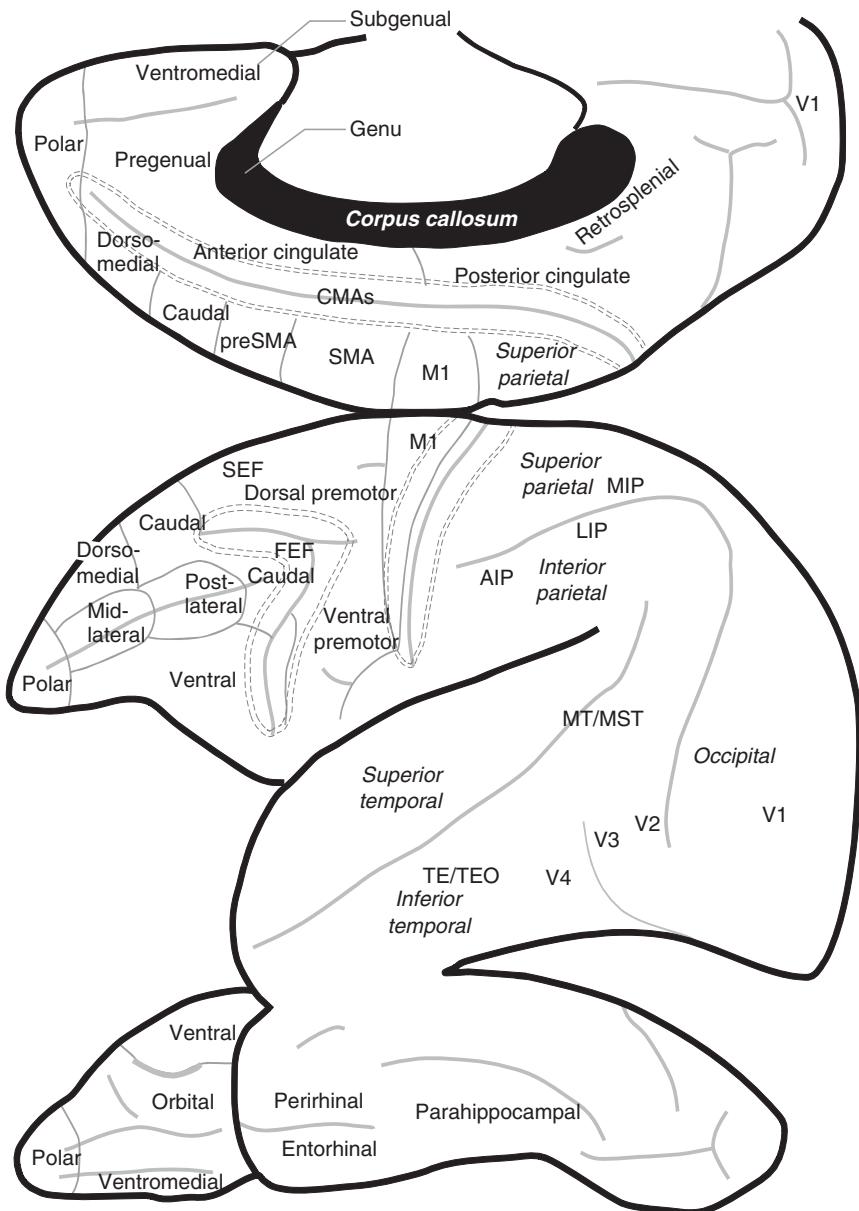


Fig. 1.4 Regional nomenclature used in this book for macaque monkeys. Format as in Figure 1.2. Abbreviations: see List of Abbreviations.

activation are so as to relate them to what we know about homologous areas in monkeys. To do this, we have used the programme MRIcro (<http://www.cabiatl.com/mricro/micro/index.html>), which takes the reported coordinates of an activation site and shows where it lies with respect to gyral and sulcal landmarks. As a result, our account of the localization of brain activations sometimes differs from that of the authors. We hope that they will forgive our presumption.

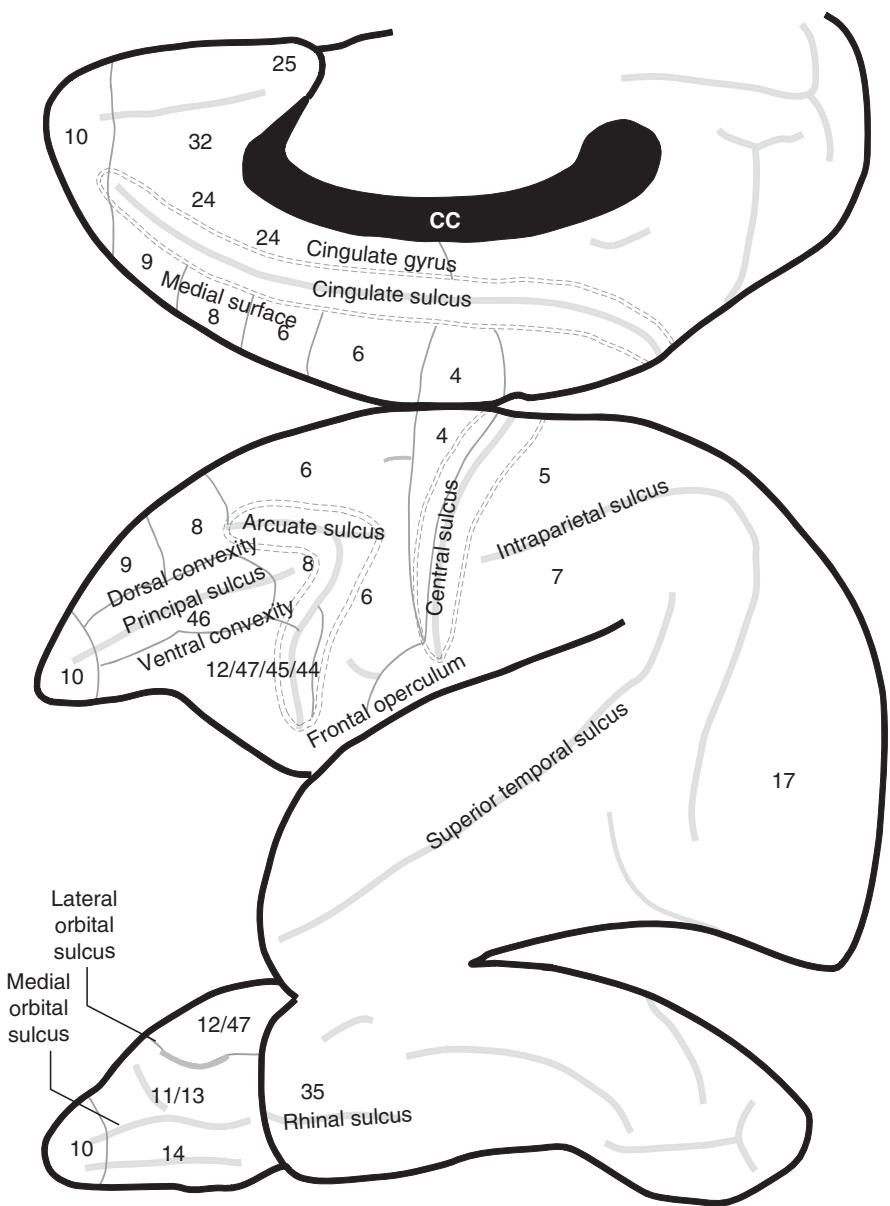


Fig. 1.5 Correspondence of the regional nomenclature in Figure 1.4 with cortical areas, selected sulci, and gyri. Format as in Figure 1.2. Abbreviation: cc, corpus callosum.

Summary

Given the variety of labels for different PF areas, we refer the reader to Tables 1.1 and 1.2. The tables and figures in this chapter call for a word of warning. It is easy enough to apply the same name to some part of the cerebral cortex in macaques and humans; it is quite another matter to establish that these areas are what their common name implies: homologues inherited from a common ancestor. Chapter 2 takes up this topic.

Fingerprints

We now turn to a key concept, which lies at the heart of our second and third aims. A successful theory of the PF cortex must explain not only what it does but also why it alone can do that. To accomplish these aims, we rely on ‘fingerprints’. This metaphor comes from Zilles and Palomero-Gallagher (2001), who used it to describe a polar plot showing the density of various neurotransmitter receptors and transporters in a cortical area. As in forensic science, neurotransmitter ‘fingerprints’ serve an identification function based on many features. Passingham et al. (2002) called the overall pattern of connections of an area its connectional fingerprint, as we do here.

Connectional fingerprints

The serious work on cortical connections began with Pandya and Kuypers (1969) and Jones and Powell (1970), and it continues to this day. Of course, findings change as the methods become more sensitive and reliable, and for other reasons, as well.

For example, the outputs of the basal ganglia have been said, at different times, to target the supplementary motor area (SMA) alone (Schell & Strick 1984); to target the primary motor cortex (area 4) and the premotor cortex (area 6) together (Kemp & Powell 1971); or to target additional areas, including the presupplementary motor area (preSMA), the cingulate motor areas (CMAs), and the granular PF cortex (Matelli & Luppino 1996; McFarland & Haber 2002). Recent evidence indicates that the outputs of the basal ganglia extend to the parietal (Clower et al. 2005) and temporal lobes (Middleton & Strick 1996), as well. No doubt, the accepted anatomy will change again some day, but for now we make do with what we have.

The connectional fingerprint of a cortical area has important consequences because its connections constrain its functions. Obviously, a cortical area cannot perform visual functions if it receives no visual inputs. Passingham et al. (2002) used the data from an anatomical database to chart the connections among different parts of the PF cortex. The database is called Cocomac (<http://www.cocomac.org/>), which refers to the *cortical connections* of the *macaque* monkey. In the latest version, it contained data from 413 studies with 39,748 connectional entries.

By using these connectional data, Passingham et al. showed that each PF area had a unique set of inputs and outputs. For each area, they plotted the strength of the connections in polar coordinates. Figure 1.6 shows two of these connectional fingerprints, one for the dorsal PF cortex (area 9) and another for the medial part of the orbital PF cortex (area 14). The circumference shows areas connected with the featured area, and the radius plots the subjective strength of each connection ranging from one to three.

Passingham et al. also used multidimensional scaling to study these connections. As illustrated in Figure 1.7A, multidimensional scaling shows that no two areas have exactly the same pattern of connections. More recently, Averbeck and Seo (2008) have also used the Cocomac database to chart the long-range corticocortical connections of the various PF areas. They confirmed that each PF area has a unique pattern of connections.

No area of the brain acts in isolation, and so we need to understand each part of the PF cortex in the context of the PF cortex as a whole. Passingham et al. (2002) therefore

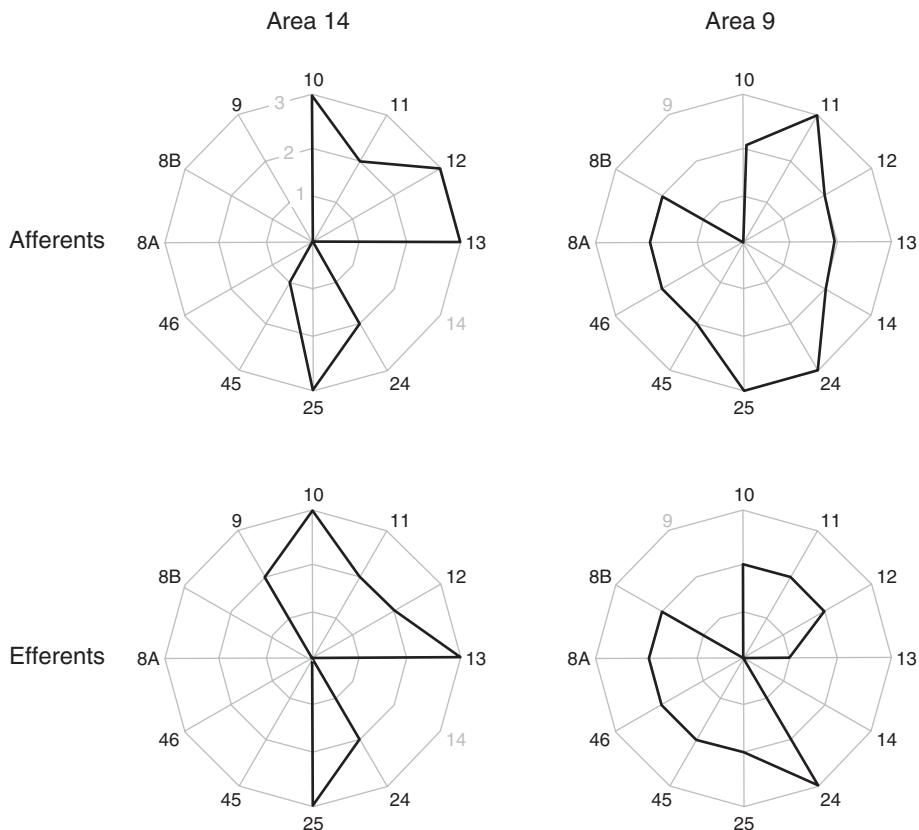


Fig. 1.6 Connectional fingerprints for the dorsomedial PF cortex (area 9) and part of the orbital PF cortex (area 14). Each polar plot shows the areas connected with areas 9 or 14 on the circumference, with the subjectively assessed intensity of the projection along the radius: light (1), moderate (2), or heavy (3). For example, the upper left plot shows that area 14 has a 'heavy' connection with area 10. Projections within an area are not included (grey labels on circumference). Reproduced from Passingham RE, Stephan KE, Kotter R. 2002. The anatomical basis of functional localization in the cortex. *Nature Review Neuroscience* 3:606–16, © 2002, with permission from *Nature Reviews Neuroscience*.

went on to use hierarchical cluster analysis to show that within the PF cortex one could identify clusters of regions that had similar connections. Averbeck and Seo (2008) used a different technique to define such clusters and came to similar conclusions.

Figure 1.7B shows five clusters within the PF cortex (Passingham et al. 2002). Like the analysis of Averbeck and Seo (2008), it depends solely on connections. However, when one combines these connection-based clusters with information about each area's location within the PF cortex, a slightly different view emerges. For this reason, we use a scheme that closely resembles the one advanced by Price and Drevets (2010). They recognized five divisions of the PF cortex: medial, orbital, caudal, dorsal, and ventral. Chapters 3–7 consider these five regions chapter-by-chapter, and Figure 1.8 illustrates them. For the most part, these demarcations agree with traditional views of the PF cortex.

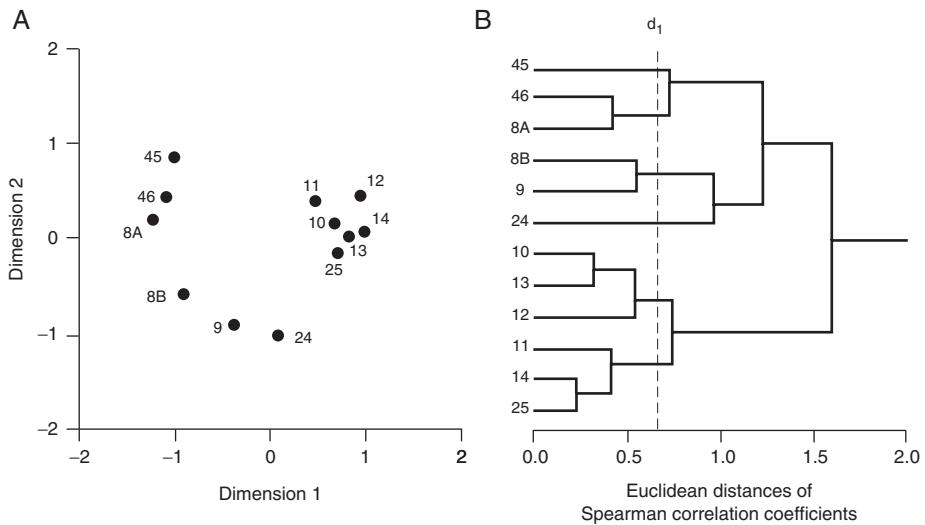


Fig. 1.7 Connectional clusters in the PF cortex. (A) Plot of two connectional dimensions with the area denoted by the number next to each point. (B) Hierarchical clustering of separation along a connectional dimension, denoted as d_1 . Reproduced from Passingham RE, Stephan KE, Kotter R. 2002. The anatomical basis of functional localization in the cortex. *Nature Review Neuroscience* 3:606–16, © 2002, with permission from *Nature Reviews Neuroscience*.

For instance, Figure 1.7A supports the inclusion of the polar PF cortex in the medial PF cortex for macaque monkeys. Each region makes up part of a larger network of areas that includes the premotor, parietal, temporal, and hippocampal cortex.

Findings about broad, distributed neural networks pose a challenge, which relates to our second and third aims. It is not enough to place a PF area within a network, one also needs to say in what way that area differs from the other areas in the same network. Take, for example, the neural network that includes the mid-lateral PF cortex (area 46) as well as several parts of the posterior parietal cortex. Lesions of these two parts of the network have dramatically different effects on behaviour.

The classical version of the delayed alternation task requires monkeys to learn to choose a food-well on the left on one trial and a food-well on the right on the next trial, and so on, thus alternating from trial to trial. Monkeys with lesions of the mid-lateral PF cortex (area 46) fail to relearn this task (Butters & Pandya 1969), but lesions of the posterior parietal cortex have no effect (Ettlinger et al. 1966). The explanation must be that although the mid-lateral PF cortex and the posterior parietal areas share many connections, especially with each other, they do not share all of their connections. The connectional fingerprints of each area point to the differences that matter.

Physiological fingerprints

The connectional fingerprint of an area shows something about the constraints and capabilities of that area. By analogy, Passingham et al. (2002) introduced the concept of functional fingerprints. They illustrated these properties with physiological data, and so we

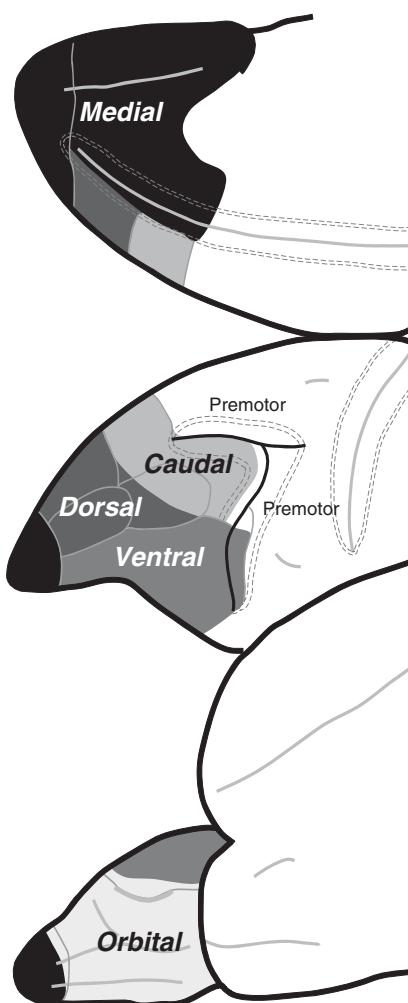


Fig. 1.8 The five regions of the PF cortex used in this book. Format as in Figure 1.2. Each of these five regions, the medial (top), orbital (bottom), caudal, dorsal, and ventral PF cortex (middle) are the topic of a later chapter.

use the phrase *physiological fingerprints* here. For one data set, they plotted five properties of cell activity: (1) auditory or visual responses; (2) proprioceptive or cutaneous responses; (3) a pattern of activity of like that of muscles; (4) a temporal correlation of activity with movements; and (5) persistent delay-period activity.

Figure 1.9C shows that the SMA and the ventral premotor cortex differ in the relative frequency of the various cell classes. For example, a higher proportion of the cells in the SMA have somatosensory responses. The figure also shows that the two areas differ in their connectional fingerprints (Figures 1.9A and B).

For a second data set, Passingham et al. (2002) plotted the preference of cells for movement sequences performed from memory or based on visual cues (Mushiake et al. 1991). The histograms in Figure 1.10 show the results for the SMA and the premotor cortex, with activity classified from one to seven. Cells in class one had complete specificity for the visual task; those in class seven had complete specificity for the memory-guided task.

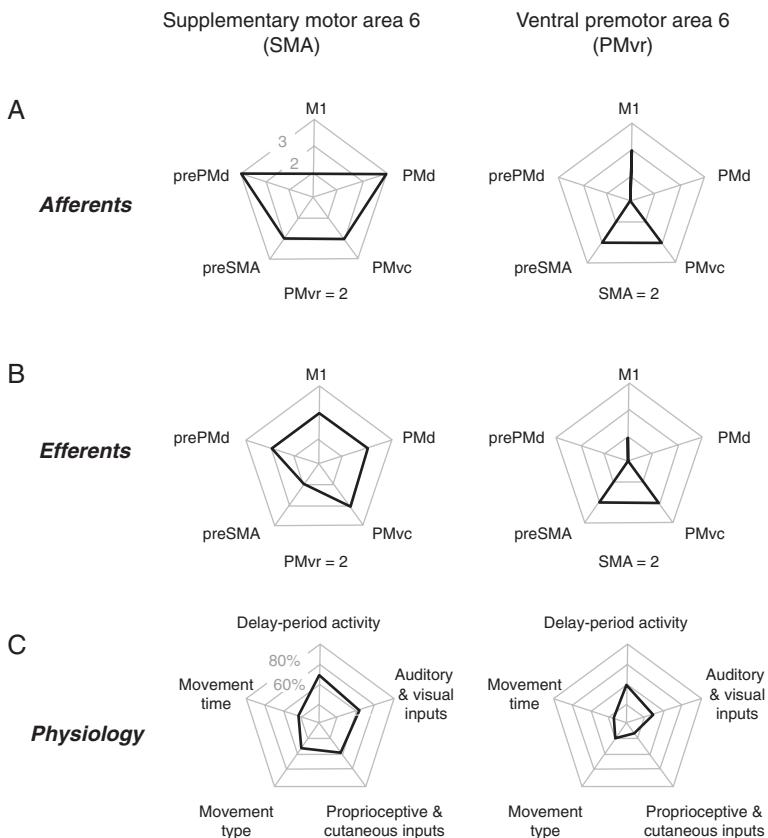


Fig. 1.9 (A, B) Connectional fingerprints for the supplementary motor area (SMA) and the rostral part of the ventral premotor cortex (PMvr). Abbreviations: M1, primary motor cortex (area 4); PMd, dorsal premotor cortex (area 6); PMvc, caudal part of the ventral premotor cortex (area 6); preSMA, presupplementary motor area (area 6); prePMd, rostral part of the dorsal premotor cortex (area 6). The equation beneath each of the polar plots gives the strength of connections between the SMA and PMvr. (C) Physiological fingerprints for same two areas. Reproduced from Passingham RE, Stephan KE, Kotter R. 2002. The anatomical basis of functional localization in the cortex. *Nature Review Neuroscience* 3:606–16, © 2002, with permission from Nature Reviews Neuroscience.

A classification of four indicates statistically equal activity. The SMA showed a preponderance of activity for the memory-guided task, with the lateral premotor cortex showing the opposite bias.

We have also plotted these data in the form of physiological fingerprints. The polar plots at the top of Figure 1.10 show the same data as do the bar charts below them, with the cell class plotted around the circumference and the proportion in each class along the radius.

Behavioural fingerprints

So far, we have implied that in order to understand the PF cortex we need comparisons: connectional fingerprints compare anatomical properties and physiological fingerprints

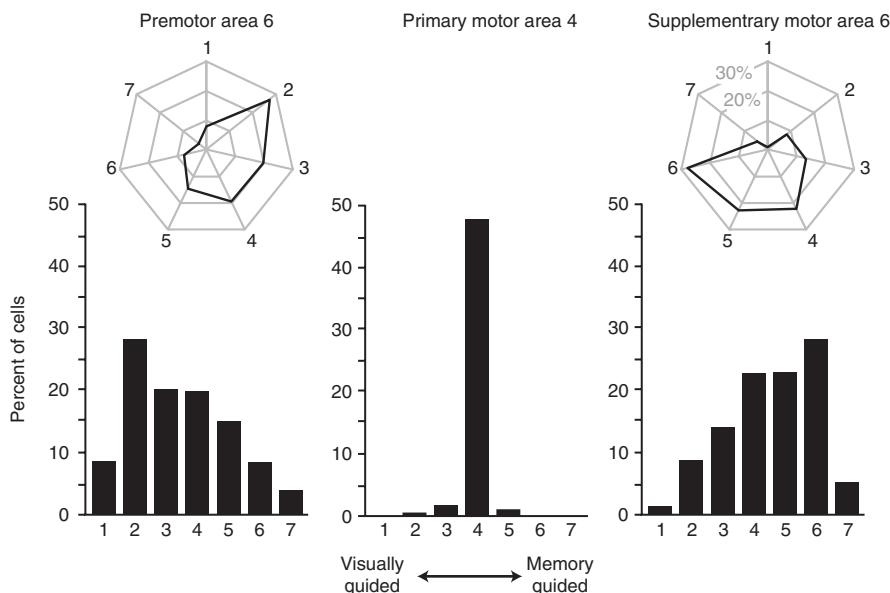


Fig. 1.10 Physiological fingerprints showing selectivity for visually-guided versus memory-guided movement sequences in the premotor cortex (area 6), the primary motor cortex (area 4), and the supplementary motor area (area 6). Cells in class 1 show complete specificity for visually-guided sequences. Cells in class 7 show complete specificity for memory-guided sequences. Cells in the other five classes show intermediate properties. The polar plots above the left and right bar graphs show the same data as the bar graphs. Bar graphs reproduced from Mushiake H, Inase M, Tanji J. 1991. *Journal of Neurophysiology* 66:705–18, © 1991 The American Physiological Society, with permission.

compare cell activity. An understanding of behaviour also benefits from comparisons. And yet the neuropsychological literature on the PF cortex often emphasizes just a few behavioural tasks. As of 2011, at least 162 papers have appeared on the delayed response task in monkeys with lesions of the PF cortex, and many of these papers deal only with that one task.

This focus has its advantages. It permits behavioural, physiological, imaging, and pharmacological experiments on the same task, for example. But the narrow focus on one or a few tasks can yield a distorted view of PF cortex function. In Chapters 5 and 6 we explain why the delayed response task and its close relative, the delayed alternation task, yield such distortions. Results from these tasks have led to the conclusion that the PF cortex functions primarily, if not exclusively, in working memory. Chapter 10 explains why we reject that theory of the PF cortex. But one does not need to know why we do so to appreciate the problem with relying on just a few tasks. Concluding, on the basis of two tasks, that the PF cortex functions in working memory is like concluding that all ripe apples are green after visiting two groves of Granny Smith apples.

We do not dispute that lesions of the primate PF cortex cause a severe and lasting impairment in the learning and performance of these tasks—or that some ripe apples are green. There must be something about the primate PF cortex that makes it necessary for

the performance of these tasks. But it takes a comparison among tasks to understand what that something is. Thus, in addition to the connectional and physiological fingerprints discussed earlier, we also need behavioural fingerprints, which involve a comparison of lesion effects among tasks. We need to understand a broad range of tasks on which monkeys with PF lesions display impairments.

Summary

The connectional fingerprint of an area constrains what it can do. Physiological and behavioural fingerprints provide insight into what that function might be. Too many theories of the PF cortex have developed from findings on one or a few tasks. In Chapter 10 we apply what we call the generality test to theories of the PF cortex, which examines whether they can account for data beyond the tasks that inspired them. In order to identify the fundamental function of the primate PF cortex, we need to rely on a broad range of findings, as epitomized by connectional, physiological, and behavioural fingerprints.

Lesions and activation

Given that imaging has made it possible to study the intact human brain, one might think that we no longer need to appeal to the effects of brain lesions when trying to understand the PF cortex. After all, as applied to human subjects, imaging has two great advantages over lesion studies. First, the peaks of activation lie in the grey matter, whereas in patients the lesions often damage the underlying white matter. Second, the peaks can, and often do, lie within specific areas. By contrast, lesions in patients commonly include many different areas.

Given these advantages, readers might wonder why we place so much emphasis on the effects of lesions. We do so because the observation of activity or activation in an area does not tell us that the subject cannot perform the task in the absence of that area. Take, for example, an imaging study by Price et al. (1999). Their subjects saw a series of pictures, one of which was designated as a target. On each trial, they had to choose which of two pictures was associated with the target. So, for example, when presented with a pair of pliers they had to choose a wrench rather than a saw. The pliers and wrench go together because they grip things, and putting them together requires semantic categorization.

Activations occurred in three places: the left middle temporal cortex, the left inferior temporal cortex, and the left ventral PF cortex. But Price et al. also scanned a patient with a complete lesion of the left ventral PF cortex. The patient could still perform the task, even though there was no activation in any of the remaining PF cortex. So we can conclude that the left ventral PF cortex is not *necessary* for performing the semantic categorization task, even though it shows activations during the performance of the task. We can also infer that the middle and inferior temporal cortex are *sufficient* for performing the task, without any contribution from the ventral PF cortex. We could only reach this conclusion by combining imaging with studying the effects of a lesion.

Unfortunately, it is only rarely possible to use this approach with humans because of the difficulty in finding patients with lesions of only one area. Although temporary lesions,

such as those caused by repetitive transcranial magnetic stimulation (rTMS), provide a useful alternative to finding patients with a given lesion, this method also has serious limitations. Much of the human cortex lies buried deep in sulci, and the stimulation cannot reach it selectively. Moreover, the precise anatomical boundaries for the stimulation effects are never known.

For this reason, we rely heavily on the effects of cortical lesions in monkeys. By using selective surgical techniques, one can remove the cortex alone, while leaving the underlying white matter intact. And one can selectively remove a particular area, especially where sulci provide useful guidance. The boundaries of the lesion can later be assessed with reasonable accuracy. As an alternative, one can inactivate an area selectively and temporarily.

Because of its greater anatomical precision, we rely heavily on experimental results from monkeys for our understanding of lesion effects. This does not mean that we ignore the results from studies of patients completely. These observations can contribute in several ways. For instance, the behavioural effects of lesions can be difficult to interpret in monkeys, and studies in human patients can help resolve these difficulties.

Take two matching tasks, for example. In the delayed matching-to-sample task, monkeys first see an object (the sample) and after a delay they have to choose the one of two objects that matches the sample. We call this the matching rule. On the delayed non-matching-to-sample task, they need to choose the other object: the nonmatching rule.

Suppose that monkeys with lesions of the PF cortex show impairments on these tasks. It could be that they cannot remember the sample or cannot recognize two objects as being the same or different, or it could be that they no longer know the task rule. One advantage of studying patients with PF cortex lesions is that we can tell them the rule and later check to see if they know it. If they cannot perform the task normally but can tell the experimenters the rule, this counts as evidence that they have either forgotten the sample or have a problem in recognizing that two objects match.

This example also points to the danger of relying on task names. The matching and nonmatching tasks have also been called ‘recognition memory tasks’. This name would be fine if a monkey could only perform these tasks in one way: by remembering and recognizing objects. Unfortunately, like many of the tasks used in monkey research, these tasks lend themselves to several alternative strategies. The monkeys could choose an object based on recognition, familiarity, or recency, depending on the details of each experiment, and sometimes the experimenters do not know how the monkeys perform the task. Specific comparison conditions could distinguish these strategies, but they have not always been used. Similarly, we later discuss experiments involving the so-called self-ordered task. In fact, it does not matter whether the subjects or the experimenter generate the order (Petrides 1995), and so the name can be misleading if taken literally.

However, so long as one is careful over the interpretation of lesion effects, this method still provides some of the most important evidence about the function of an area. The gold standard is called a double dissociation of function. This means that a lesion in one area impairs performance on one task but not on a different one, and that a lesion in some

other area has the opposite effects for both tasks. For example, lesions of the ventral PF cortex disrupt the ability of the monkeys to perform one kind of strategy task (Baxter et al. 2009), whereas lesions of the orbital PF cortex do not (Baxter et al. 2007). By contrast, orbital PF cortex lesions disrupt performance on a devaluation task (Izquierdo et al. 2004), whereas lesions of the ventral PF cortex do not (Baxter et al. 2009). Chapters 4 and 7 explain these tasks and their implications in some detail, but even without these particulars one can see that the results establish some sort of double dissociation of function.

Notwithstanding these and a few other examples, Gaffan (2002) has pointed out that double dissociations of this sort are less common than usually supposed for the PF cortex. And Wilson et al. (2010) have emphasized that manipulations affecting the PF cortex as a whole usually produce much larger effects than those mainly affecting parts of it. These findings support the view that the PF cortex works as a whole, and Chapter 8 takes up this topic.

Summary

In a field dominated by imaging experiments, many neuroscientists seem to think that an understanding of lesion effects has little to offer when considering the function of a cortical area. We have used an example from the imaging literature to refute this idea: imaging activations show something about information processing, but they do not demonstrate a necessary role in some task or function, as lesion studies do.

Lesions and activity

The previous section contrasted lesion and imaging methods; this section contrasts lesion and cell-recording methods. These two methods tell us different things. Because they do so, the effects of lesions do not always appear to match up with the cell activity that occurs in the same area. We discussed one example earlier. In monkeys, lesions of the mid-lateral PF cortex (area 46) and the posterior parietal cortex have different effects, even though these two areas have connections with each other and have similar cell activity during various tasks. We mentioned earlier that monkeys with mid-lateral PF cortex lesions fail to learn the delayed alternation task, whereas monkeys with large lesions of the posterior parietal cortex perform the task normally. Nevertheless, cells in both the mid-lateral PF cortex (Kojima & Goldman-Rakic 1984) and the posterior parietal cortex (Chafee & Goldman-Rakic 1998) show sustained activity during delay periods, an interval when the monkeys must remember the information that they need to perform the task. As a result, the cell activity and lesion effects match up pretty well in the mid-lateral PF cortex (sustained activity *and* lesion effects), whereas for the posterior parietal cortex they do not (sustained activity but no lesion effect).

As another example, consider the medial and lateral groups of premotor areas, which have extensive interconnections (Luppino et al. 1993). Lesions of the medial areas severely disrupt self-generated movements, defined as movements made without prompts from visual cues. Lesions of the lateral premotor areas do not have this effect (Thaler et al. 1995); they affect visually cued movements instead. How could this be so, given that many cells in both the medial and lateral premotor areas discharge whether movements

are visually cued or self-guided? Figure 1.10 shows that many cells in both regions fall into class four, which indicates statistically identical activity for the two forms of guidance. Other cells show a bias, but they still have significant activity for both tasks.

To answer this question, one needs to appreciate that lesions show us what other areas of the brain can or cannot do in the absence of the lesioned area. Lesions not only remove the computational resources of the damaged area, they also remove its inputs to other areas, among other influences. In the intact brain, cells in lateral premotor cortex show increased activity when the animal performs self-guided movements (classes five to seven in Figure 1.10) (Mushiake et al. 1991). So, one might expect that the lateral premotor areas could take over self-generated movements in the absence of the medial premotor areas. But suppose that these cells get inputs from the medial premotor areas and that these connections produce the cells in classes five to seven. Then, in lesioned animals, these cells would no longer have the same properties as they do in normal animals. As a result, the lateral premotor area could not ‘take over’ self-guided movements in the absence of the medial premotor areas.

This line of thinking explains one reason that areas can show activity for some behaviour even when they do not play a necessary role in that behaviour. Similar principles apply to the PF cortex. In a typical version of the conditional visuomotor task, one picture instructs a monkey to make one kind of response and a second picture instructs a different response. Cells encode these picture–response mappings in both the mid-lateral PF cortex and the ventral PF cortex areas (Asaad et al. 1998). Yet the effects of lesions in these two areas differ. Lesions of the ventral PF cortex produce a severe impairment on this task (Wang et al. 2000), but lesions of the mid-lateral PF cortex have only mild effects (Petrides 1987). We can reconcile these findings in the same way as for the first example. A lesion of the ventral PF cortex cuts off most of the inputs from the inferior temporal cortex to the mid-lateral PF cortex (Ungerleider et al. 1989; Webster et al. 1994), and so the mid-lateral PF cortex cannot ‘take over’ the function.

As a result of the strengths and weaknesses of both lesion and cell-recording methods, we need to compare cell activity with the effects of brain lesions in order to gain the most benefit from both sources of information.

Another kind of activity that comes up from time to time in the book involves intracortical microstimulation. This method introduces electrical currents through the same kind of electrodes used to study the activity of single cells. It thus generates activity synchronously in hundreds of cells, at the least. The comparison with normally occurring discharges is complicated, but the method provides useful information on the assumption that it roughly mimics normal activity.

Summary

The effects of cortical lesions do not always match up with cell activity in the way that one might expect. In this section, we have explained one reason that these apparent mismatches occur. Both lesion effects and cell activity depend on an area’s connections, but in different ways. Cell activity reflects either the receipt of information via connections or information processing within an area. These results thus reflect the neural correlates

of a behaviour, whereas lesion effects reveal an area's necessary contribution to that behaviour.

Activity and activation

In later chapters, we liberally mix discussions of regional brain activations with findings about cell activity. However, this combination requires caution for two reasons: vascular artefacts and uncertainty about the relationship between cell activity and imaging activations.

First, the blood oxygen-level dependent (BOLD) signal is a vascular signal, and so it is sensitive to the location of major arteries. The BOLD signal is also potentially contaminated by the location of the veins and venous outflow (Turner 2002). For these reasons, among others, the peak of the BOLD signal has only a very rough spatial correspondence with the location of the underlying brain activity (Kim et al. 2004).

Second, we know very little about the relationship between imaging activations and cell activity. A direct comparison of imaging and cell activity in monkeys would help, but to have any value in understanding the PF cortex this comparison would have to be made for a sparsely coded network. In a sparsely coded network, nearby cells have diverse properties; in a densely coded network, most cells do much the same thing. Results from densely coded networks, such as sensory or motor areas, are potentially misleading because of this relative homogeneity. We have only a small amount of imaging data on sparsely coded networks in monkeys, such as the PF cortex or the hippocampus (Nakahara et al. 2002; Orban et al. 2004). So we must make do by applying general principles.

Imaging experiments measure the BOLD signal. A BOLD response can occur in the absence of action potentials (Logothetis 2002), and the BOLD signal can differ between experimental conditions when spiking activity does not. For example, Maier et al. (2008) studied both BOLD activation and single-cell activity in the primary visual cortex of monkeys. They used a perceptual manipulation called generalized flash suppression. When moving dots appear abruptly around a visual target stimulus, they suppress the perception of the target stimulus. The suppressive stimuli did not affect the single-cell activity in visual cortex, but they did affect the BOLD signal. This finding suggests that the BOLD signal is sensitive to modulatory effects (Logothetis 2008), which are probably mediated by inhibitory synaptic inputs or by excitatory ones below the threshold for driving cell activity.

A particularly well-studied example involves the cerebellum. Although synaptic activations and the BOLD signal correlate closely in cerebellar cortex, the activity of its output neurons, the Purkinje cells, does not (Thomsen et al. 2004). Synaptic inputs to Purkinje cells, rather than the activity of Purkinje cells, drive the BOLD signal (Gold & Lauritzen 2002). Oxygen consumption increases linearly with the local field potentials induced by both of the major inputs to Purkinje cells: climbing fibres (Offenhauser et al. 2005) and parallel fibres (Thomsen et al. 2009), and these potentials reflect synaptic inputs rather than the discharge activity of Purkinje cells.

Thus, most of the evidence supports the conclusion that the signal measured in imaging studies does not reflect neuronal activity directly, but instead reflects synaptic inputs. Sometimes the net synaptic input (activation) correlates with neuronal activity, but often it does not. For this reason, we distinguish cell *activity* from regional *activations* throughout this book. We take activations to reflect synaptic influences rather than the discharge rate of individual cells (Logothetis 2002).

Meta-analysis

We mentioned earlier the danger of excessive reliance on one or a few tasks in interpreting lesion effects. The same caution applies to cell recording and imaging. In an often-quoted study (Funahashi et al. 1989), monkeys fixated a central light spot and a cue appeared at one of eight places. After a delay period, a ‘go’ cue triggered a saccadic eye movement to the cued location. Of the cells with significant activity during the delay period, the majority (~80%) encoded the location of the cue. It is understandable that many neuroscientists saw this result as consistent with the idea that the cells encoded remembered locations.

But it is dangerous to draw this conclusion on the basis of one task alone. Cell activity depends to some extent on a monkey’s training history. For example, Freedman et al. (2006) trained monkeys to distinguish pictures of cats and dogs. They found stronger selectivity for stimuli presented in orientations used during training than for different orientations. This finding is hardly surprising because animals (and their cerebral cortex) learn from experience.

With this principle in mind, the results of Funahashi et al. (1989) provide less support for their interpretation than they thought. If one only studies cell activity during a simple spatial memory task, it will seem as though many cells encode remembered locations.

But one can only test this impression by comparing cell activity on other tasks. For example, cell activity during the delay period might reflect places that monkeys attend to as well as those that they remember. So Lebedev et al. (2004) trained monkeys both to remember a location and to attend somewhere else. Of the PF cells with activity that showed selectivity for a location, 61% encoded the attended location alone, with a role in memory being ruled out. Only 16% of the cells encoded the remembered location alone, and the remainder had mixed properties. Only the comparison among tasks could show that the interpretation of neuronal activity in term of spatial memory was, for the most part, mistaken.

In Chapters 8 and 9 we recognize the importance of such comparisons by tabulating results from many tasks. Table 8.1 presents a compilation of lesion effects in monkeys, and Table 8.2 presents a selection of cell-activity properties. Table 9.10 does something of the sort for imaging activations in people. One can only reach a conclusion about the fundamental function of the PF cortex by taking into account results from a broad array of tasks.

This approach resembles one that is commonly used in the imaging literature. Because results can be reported in a common anatomical coordinate frame, one can perform a meta-analysis, which involves a synthesis of the data from tasks that cause activation in an area. A meta-analysis is a physiological fingerprint by another name.

Summary

Although Chapters 3–7 do not use polar plots to illustrate connectional, physiological, or behavioural fingerprints, they convey the same principle through more conventional means. For neuroanatomical data, they present the connections of a particular area on maps of monkey brains. They emphasize that understanding the PF cortex requires a comparison of connections among different brain areas (connectional fingerprints), as well as a comparison of lesion effects (behavioural fingerprints) and both activity and activations for a wide variety of tasks (physiological fingerprints). Although we owned up in the Preface to cherry-picking data, we hope that readers will agree that we have tried to pick a lot of cherries.

This section has contrasted cell recording and imaging results. Imaging, like all methods, has limitations. But it has at least three major advantages over studies of cell activity:

1. Imaging allows one to survey most of the brain simultaneously.
2. The peak location for the BOLD signal presumably reflects the peak density of signals of a particular functional type, whereas cell recording will detect a type of activity wherever it occurs.
3. The BOLD signal appears to reflect synchronized activations especially well. Parkes et al. (2006), for example, combined electroencephalography (EEG) and functional imaging and found a close correlation of synchrony and activation. The relation between the BOLD signal and field potentials is closest in the low-frequency range (Kayser et al. 2004).

Cell recording has some advantages over imaging, however. It shows directly what an area's information-processing elements encode. It can demonstrate distinct properties even when diverse and intermixed neuronal populations could not be detected in imaging experiments, which is of particular importance for sparsely coded neural networks like the PF cortex. Finally, cell recording can distinguish increases in activity from decreases, whereas imaging cannot. (Imaging can distinguish increases from decreases in activation, but not in activity.) Discussions of the imaging literature rarely note, for example, that an increase in activation might reflect the suppression of the output from an area, and this is especially true of sparsely coded networks.

Conclusions

This book adopts a comparative approach to advance a proposal on the fundamental function of the primate PF cortex. It has five explicit aims: to describe the advantages conferred by the PF cortex, to say how its connections lead to its unique function, to consider how it works as a whole, to account for activations during cognitive tasks in humans, and to explain how our proposal differs from others in the literature as well as how it can be tested.

To fulfil the first aim, Chapter 2 compares the PF cortex in a diversity of species, living and extinct. To accomplish the second aim, Chapters 3–7 each start with a summary of

connections for a major part of the PF cortex. Each of these chapters concludes with a brief but specific proposal concerning the function of that part. To fulfil the third aim, Chapter 8 builds on the proposals in Chapters 3–7 to advance a proposal for the fundamental function of the PF cortex as a whole. To achieve the fourth aim, Chapter 9 explains how we account for imaging activations as people perform complex cognitive tasks. Finally, for the fifth aim, Chapter 10 compares our proposal with others in the literature, advances some ways to test it, and suggests some observations that might contradict it.

Chapter 2

Evolution of the primate prefrontal cortex

Overview

The PF cortex evolved in phases. One occurred in early mammals and produced the agranular PF areas, which all mammals share. These areas improve foraging choices among actions (Chapter 3) and objects (Chapter 4) based on predicted outcomes. Another advance occurred in early primates and produced the first granular PF areas. These animals adopted a nocturnal life confined to the fine branches of trees, where they searched for, chose among, and grasped their food items, feeding with a novel technique that required coordinated movements of their head and one hand. Their new PF areas contributed to choosing food items based on current biological needs and particular previous choices (Chapter 4), as well as maintaining attention to them in a cluttered environment (Chapter 5). Later, during the evolution of anthropoid primates, additional granular PF areas appeared as these species and their brains increased in size. They foraged by day, relying on the recently evolved primate fovea and improved colour vision. As a result, these animals could process the order of events in space and time (Chapter 6) and detect the signs of resources (Chapter 7) better than their ancestors. By exploiting rich resources dispersed over large home ranges, anthropoids faced severe resource volatility, predation, and competition. Their new PF areas enabled them to decrease the number of risky and unproductive foraging choices by using single events to choose foraging goals (Chapter 8).

Introduction

This chapter explores some consequences of the fact that the granular PF cortex first appeared in early primates and that primates alone have this kind of cortex (Preuss 2007a).

Because of its name, some neuroscientists have assumed that conclusions about the evolutionary history of the granular PF cortex depend exclusively on cytoarchitecture. And one might argue that this is a thin reed upon which to lean, given the importance of the claim. Fortunately, many additional traits support the idea that the granular PF cortex evolved in primates. Later we will set out four of them: the spatial layout among cortical areas; the

pattern of projections from the PF cortex to the striatum; the distribution of sensory inputs; and the autonomic effects that are evoked by electrical stimulation of the cortex.

Figure 2.1 illustrates our view of the homologies among PF areas in humans, rhesus monkeys, and laboratory rats—two anthropoid primates and a muroid rodent—which owes a great deal to the pioneering work of Preuss and Goldman-Rakic (1991a). By

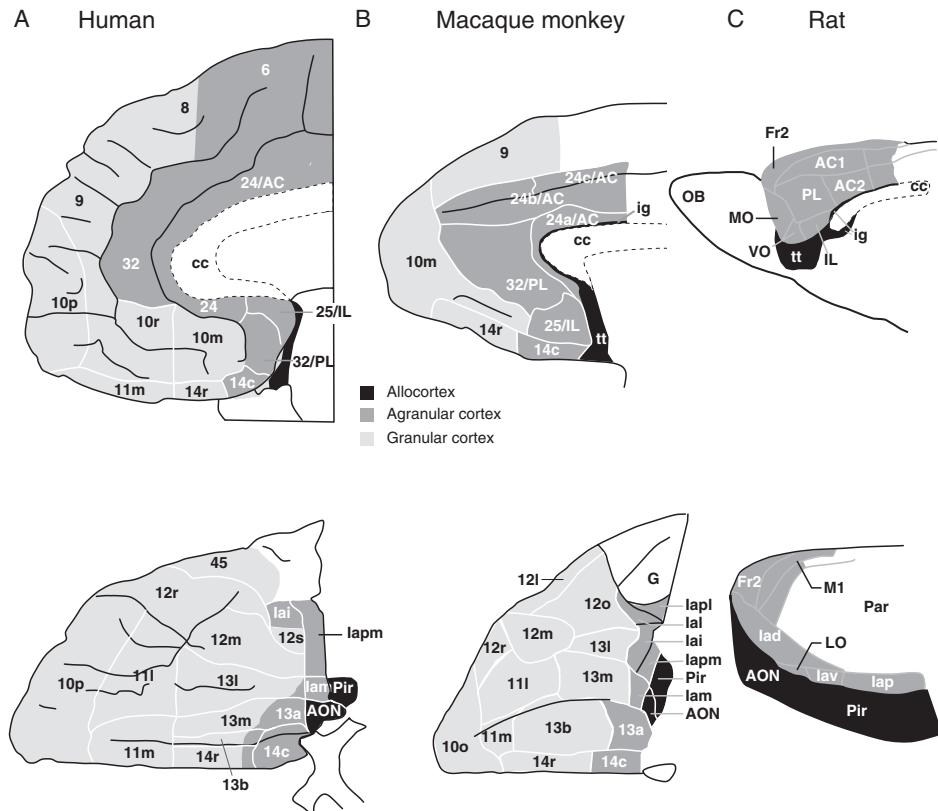


Fig. 2.1 (A) Medial (top) and orbital (bottom) areas of the human frontal cortex (Öngür et al. 2003). (B) Medial (top) and orbital (bottom) areas of the macaque frontal cortex (Carmichael & Price 1994). (C) Medial (top) and lateral (bottom) areas of rat frontal cortex (Palomero-Gallagher & Zilles 2004). Rostral is to the left in all drawings. Top row: dorsal is up in all drawings. Bottom row: in (A) and (B), lateral is up; in (C), dorsal is up. Not to scale. Abbreviations: AC, anterior cingulate cortex; AON, anterior olfactory ‘nucleus’; cc, corpus callosum; Fr2, second frontal area; la, agranular insular cortex; ig, induseum griseum; IL, infralimbic cortex; LO, lateral orbital cortex; MO, medial orbital cortex; OB, olfactory bulb; Pir, piriform (olfactory) cortex; PL, prelimbic cortex; tt, tenia tecta; VO, ventral orbital cortex. Subdivision of areas are labelled caudal (c); inferior (i), lateral (l), medial (m); orbital (o), posterior or polar (p), rostral (r), or by arbitrary designation (a, b). (A) Adapted from Öngür D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology* 460:425–49 © 2003, with permission from John Wiley and Sons. (B) Adapted from Carmichael ST, Price JL. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *Journal of Comparative Neurology* 346:366–402 © 1994, with permission from John Wiley and Sons. (C) Adapted from Palomero-Gallagher N, Zilles K. Isocortex. In *The Rat Nervous System*, ed. G Paxinos, pp. 729–57. San Diego, CA: Elsevier Academic Press.

homologies, we mean areas that occur in related species because of inheritance from a common ancestor. The figure shows in light grey the PF areas that evolved uniquely in primates: the granular PF cortex. These granular areas appear in human and monkey brains, but not in rat brains. Rats have only agranular PF areas, which the figure depicts in dark grey for all three species. We have chosen these three species simply because almost all of our knowledge about the PF cortex depends on studies of their brains.

The agranular PF areas include the infralimbic, prelimbic, agranular insular, agranular orbital, and anterior cingulate cortex. Many of these areas go by different names in different species. For example, the infralimbic cortex of rodents corresponds roughly with area 25 in primates, which von Bonin and Bailey called area FL (Figure 1.1).

We know that many neuroscientists believe that rats have much the same PF cortex as primates do. They insist either that rodents have a replica-in-miniature of the primate PF cortex or that they have an amalgam of all of its properties packed into their small agranular areas (Kolb 2007; Seamans et al. 2008; Schoenbaum et al. 2009). We take a different view, but one proposition should find universal acceptance. No one doubts that at some point in evolutionary history some of our ancestors lacked a granular PF cortex. Yet now we have one. Given this historical fact, it seems reasonable to ask what advantages it brings.

Although not everyone agrees with the homologies depicted in Figure 2.1, no one seriously disputes the fact that modern rodent brains lack a granular PF cortex. For other mammals, this has been in some dispute. There have been claims of a granular PF area in dogs (Rajkowska & Kosmal 1988) and cats (Rose & Woolsey 1948), but when we examine the supposedly granular areas in histological material ourselves, they look much like the agranular areas in monkeys and rodents.

This disagreement probably results from the lack of observer-independent architectonic methods, as explained in Chapter 1. When Mackey and Petrides (2010) addressed this issue in macaque and human brains, they found that some areas that have been traditionally classed as agranular frontal areas actually have a weakly increased density of cell bodies in layer 4 compared to the most caudal areas. That is, these areas have a weakly dysgranular cytoarchitecture rather than a purely agranular one. So reports of a granular PF cortex in carnivores and other nonprimate mammals probably reflect this property. All neuroanatomists agree that the thickness of layer 4 consistently increases as one goes from caudal to rostral along the orbital and medial surfaces of the frontal lobe. So the issue of whether the agranular cortex completely lacks layer 4 is of little importance. We can consider areas with layer 4 densities below a given threshold as sufficiently agranular for our purposes (Figure 2.2).

Despite the lack of a granular PF cortex in rats, some neuroscientists have argued that the medial part of the rat frontal cortex is homologous with the mid-lateral PF cortex (area 46) in primates (Kolb 2007; Seamans et al. 2008), even though the latter is a granular area (also known as the dorsolateral or periprincipal prefrontal cortex). Similarly, some contend that a lateral part of the rat frontal cortex is homologous with the entire orbital PF cortex in primates, including its granular parts (Kolb 2007; Schoenbaum et al. 2009). The argument rests on similarities in anatomy, physiology, and neurochemistry or on asserted similarities between the effects of lesions in rats and monkeys.

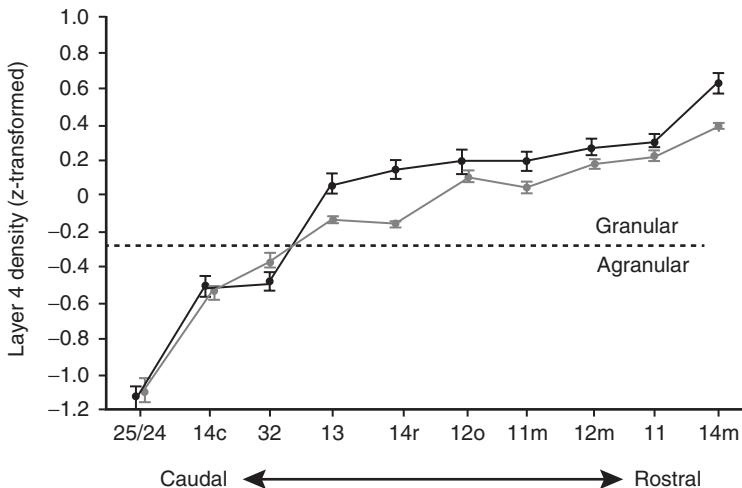


Fig. 2.2 Normalized density of cell layer 4, as a function of a caudal to rostral progression of frontal areas in monkeys (black line) and humans (grey line). Error bars: SEM. Reproduced from Mackey S, Petrides M. Quantitative demonstration of comparable architectonic areas within the ventromedial and lateral orbital frontal cortex in the human and the macaque monkey brains, *European Journal of Neuroscience* 32:1940–50, © 2010, John Wiley and Sons, with permission.

But one cannot infer homologies from similarities of the kind that are usually cited. As Preuss (1995) has explained, one needs diagnostic features, which are features that distinguish one group of cortical areas from others. For example, the rat agranular PF cortex has many similarities with the granular PF cortex areas of monkeys, such as cells that encode valuations. But all three groups of areas—the agranular PF cortex in rats and both the agranular and granular PF cortex in monkeys—share these properties, as do other cortical areas. So they do not help us understand the evolution of the PF cortex or establish homologies among its areas. For example, it is irrelevant to these ends that properties of the agranular areas in rats resemble those of the granular PF cortex in primates, if they also resemble those of the *agranular* PF cortex in primates.

Some have claimed that a connection with the mediodorsal nucleus of the thalamus (MD) is a diagnostic feature of granular PF cortex (Rose & Woolsey 1948; Akert 1964; Uylings et al. 2003). But the MD nucleus projects to virtually all of the frontal lobe, granular and agranular areas included. So connections with the MD nucleus cannot be taken as a diagnostic feature, and thus they have little or no bearing on the issue of homology.

For a while, it was thought that dopaminergic inputs characterized the granular PF cortex (Divac et al. 1978; Porrino & Goldman-Rakic 1982). But these inputs also terminate in agranular parts of the PF cortex and in premotor areas, as well as throughout much of the cortex beyond the frontal lobe. In fact, in primates, the dopaminergic inputs to premotor cortex and posterior parietal cortex are stronger than those to most of the granular PF cortex (Gaspar et al. 1992; Williams & Goldman-Rakic 1998). And so dopaminergic inputs do not help us identify the PF cortex across species.

Finally, lesion results have been advanced, such as those for the delayed response task. Lesions of the medial frontal cortex in rats cause an impairment on this task (Kolb et al. 1974), as do lesions of the granular PF cortex in monkeys (Goldman et al. 1971). But lesions of the anterior cingulate cortex also lead to an impairment in monkeys (Meunier et al. 1997). So, again, the feature is not a diagnostic one. We return to this issue in more detail in Chapter 10, emphasizing that the impairments in rats and monkeys, although superficially similar, differ in important ways.

Notice that we do not say that primates have a prefrontal cortex whereas other mammals do not. We accept that nonprimate mammals have areas that one can reasonably call prefrontal. Chapters 3 and 4 incorporate these agranular areas within the medial and orbital PF cortex. But we reject the idea that nonprimate mammals have a replica-in-miniature or amalgam of the primate PF cortex. Nonprimate mammals lack the granular PF cortex of primates as well as any areas that perform its fundamental function. By neglecting these concepts, the literature contains many instances of mixing results from nonhomologous areas, such as when findings from the mid-lateral PF cortex (area 46) of a primate are cited in support of some conclusion that pertains to the medial frontal cortex of a rodent. This is not the best way forward.

Our conclusions concerning homologies should not generate as much controversy as they often do. Take the visual cortex as an example. All primates share 10–20 visual areas and some have more (Kaas 2006). To highlight just one, an area called either MT or V5 has sophisticated specializations for analysing visual motion at the fovea. Rats have many fewer visual areas (Rosa & Krubitzer 1999; Lyon 2007), and they lack a fovea. It is simply not plausible that the small number of visual areas in rats replicate all of the functions of the 10–20 visual areas in primates. For one thing, the fine-grained analysis of foveal motion would be especially unexpected in a species that lacks a fovea.

As another example, consider the auditory cortex of echolocating bats. These animals use a sonar-like system to detect the distance and velocity of their insect prey. The bat auditory cortex has many specialized areas for processing the acoustic signals involved in echolocation, including the analysis of frequency-modulated sounds, Doppler shifts, and so forth (Suga et al. 1997; Fitzpatrick 1998). If some cells in the auditory cortex of rats also respond to similar sounds, this would not mean that they perform the same functions as auditory cells in bats. Indeed, it would be odd to imagine that they do so because rats do not track their foods with echolocation. Again, the idea that the small number of auditory areas in rats have all of the same functions and properties as the large number of specialized areas in echolocating bats lacks plausibility.

Few neuroscientists dispute the idea that echolocating bats have new auditory areas compared to their last common ancestor with rats, or that primates have new visual areas to go along with their advances in visual acuity and colour vision. And the idea that these new areas support new functions, such as the analysis of foveal motion or echolocation, has gained wide acceptance. So it is surprising that the same neuroscientists tend to baulk at the idea that primates have new prefrontal areas and that these areas perform novel functions.

Part of the problem comes from using the word *new* for areas or functions. It has been suggested that new areas appear by replication and subsequent differentiation

(Krubitzer & Huffman 2000). If so, then it is reasonable to assume that some of these new areas differentiate less than others; and we can recognize the more conservative areas as homologous when they occur in many mammalian species. However, in doing so, we need to recognize that most evolutionary change involves modification of homologues and therefore that absolute equivalence among species is unrealistic.

Compared to these relatively conservative areas, other products of the replication differentiate more and therefore deserve the designation new. As they differentiate, they come to perform new functions, thus providing an advantage over the ancestral condition. However, when these new areas evolve, they will share properties with nearby areas and will usually have axonal connections with them. And so it is not surprising that the granular and agranular parts of the PF cortex share many features. But we should not conclude on this basis that they are either homologous or analogous. The granular PF cortex evolved specifically in primates, and it developed to support primate-specific abilities.

Strepsirrhine PF cortex

The most telling evidence on the evolution of the primate PF cortex comes from the study of bushbabies (*Galago*, also known as *Otolemur*). Given the importance of this evidence, we review it in detail. However, the reader can get the gist of the argument from the summary at the end of this section.

The discussion necessarily uses some terms that may not be familiar to all neuroscientists, and so Table 2.1 lists them for ease of reference. Key names for groups of primates include prosimian, strepsirrhine, haplorhine, and anthropoid. At one point in evolution, primates split into strepsirrhine (wet-nose) and haplorhine (dry-nose) lineages. The strepsirrhines include lemurs, lorises, and bushbabies and make up most of the primates called prosimians. Haplorhine primates include tarsiers (also prosimians) and anthropoids. Anthropoids include all of the New World monkeys (platyrhines) as well as Old World monkeys, apes, and humans (collectively, catarrhines).

In what follows, we assume that features shared by modern bushbabies and anthropoids were probably present in their last common ancestor. Because that ancestor was an early primate, we suppose that these features also characterized early primates. We also assume that features found in anthropoids but not in bushbabies probably evolved in anthropoids. As always, independent evolution continues apace once lineages diverge, so bushbabies probably have adaptations that anthropoids lack, as well.

Preuss and Goldman-Rakic (1991a) argued that the bushbaby cortex lacked a homologue of the mid-lateral PF cortex (area 46), among several other granular PF areas. Instead, they identified a homologue of the caudal PF cortex (area 8) and the granular parts of the orbital PF cortex. Preuss and Goldman-Rakic supported their conclusion with a variety of arguments, including a comparison of the connections in bushbabies and macaque monkeys (Preuss & Goldman-Rakic 1991b). They also considered the work that others had done on lemurs, another strepsirrhine primate. However, most of their evidence comes from a study of the architectonics of the frontal cortex in bushbabies and

Table 2.1 Biological terminology used in this chapter

Term	Meaning
Advanced	Differing from the ancestral condition, divergent
<i>Aegyptopithecus</i>	An extinct anthropoid, near the early catarrhines
Anthropoid	Monkeys, apes, and humans
<i>Carpolestes</i>	An extinct plesiadapiform
<i>Chilecebus</i>	An extinct anthropoid, near the first platyrhines
Catarrhine	Old World primates (Old World monkeys, apes, and humans), diverged from platyrhines.
Haplorrhine	Tarsiers and anthropoids; diverged from strepsirrhines
Homology, homologous	Descended by inheritance from a last common ancestor, contrasts with similarities due to parallel or convergent evolution
Old World monkey	A group of catarrhine primates, including macaques, baboons, vervets (green monkeys), mangabeys, guenons, mandrills, and red-tail monkeys
<i>Parapithecus</i>	Extinct anthropoid, near the first anthropoids. Also called <i>Simonsius</i>
Platyrhine	New World monkeys, including marmosets, squirrel monkeys, owl monkeys, and capuchin monkeys; diverged from catarrhines
Plesiadapiform	Extinct mammals, either early primates or near relatives of early primates, including <i>Carpolestes</i>
Primitive	Resembling the ancestral condition
Prosimian	Strepsirrhine primates and tarsiers; not a natural group
Strepsirrhine	Most prosimian primates, including lemurs, lorises, and bushbabies; diverged from haplorhines

macaques. A more recent study of bushbaby brains has confirmed their analysis for the most part (Wong & Kaas 2010).

Cortical architectonics

Figure 2.3 shows the map that Preuss and Goldman-Rakic produced for the bushbaby frontal cortex. In this section, we give a detailed account of their analysis for readers interested in the anatomical details.

First, Preuss and Goldman-Rakic identified the agranular areas of the premotor cortex (area 6). The cortex immediately rostral to area 6, on the lateral surface of the bushbaby hemisphere, includes a distinctive area with a ‘very thick, dense’ layer 4 and myelinated fibre bundles that run from the subcortical white matter toward layer 4, where they disperse into the more superficial layers.

Preuss and Goldman-Rakic concluded that this area, which they called the posterior granular area (GrP) (Figure 2.3), is homologous to area 8 of macaque monkeys and humans. Electrical stimulation of this area evokes eye movements both in bushbabies (Wu et al. 2000) and macaques (Bruce et al. 1985), and this finding supports the conclusion that area GrP in bushbabies includes the frontal eye field (FEF).

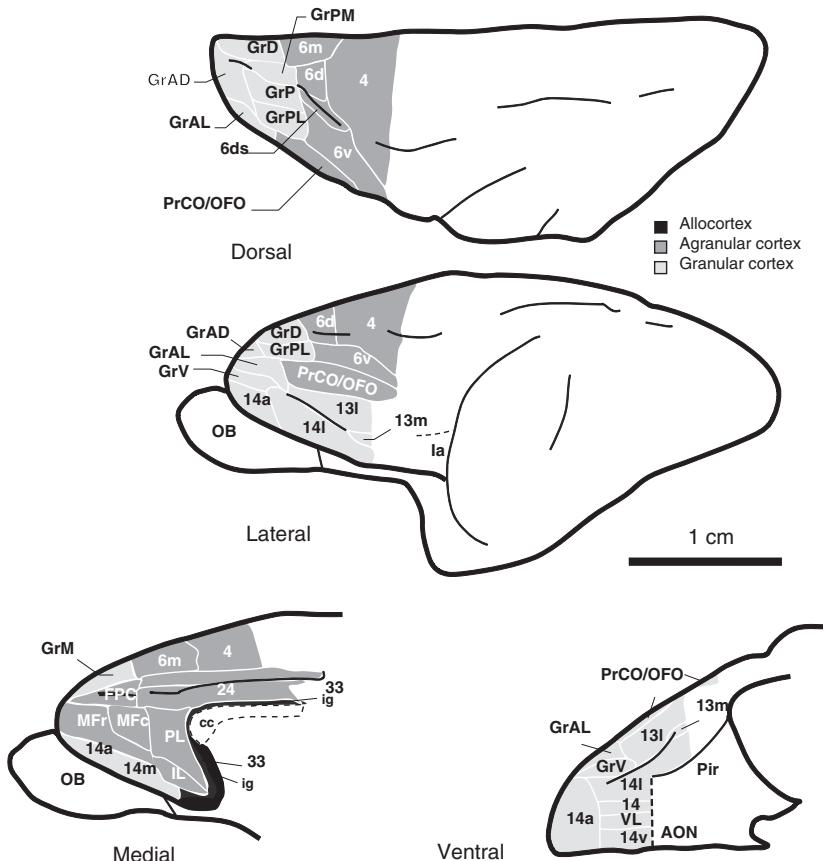


Fig. 2.3 Architectonic map of the frontal cortex of bushbabies. Rostral is to the left in all drawings. Dorsal view (top): medial is up; lateral view (middle), dorsal is up; medial view (lower left), dorsal is up; ventral view (lower right), lateral is up. Abbreviations as in Figure 2.1 and as follows: Gr, granular areas, divided according to anterior (A), dorsal (D), lateral (L), medial (M), posterior (P); PrCO/OFO, precentral opercular area/orbitofrontal opercular area; 6ds, sulcal part of dorsal area 6; FPC, frontopolar cingulate cortex; MF, medial frontal cortex; VL, ventrolateral cortex. Adapted from Preuss TM, Goldman-Rakic PS. Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirrhine primate *Galago* and the anthropoid primate *Macaca*. *Journal of Comparative Neurology* 310:429–74 © 1991, John Wiley and Sons, with permission.

Area GrP is flanked by the postero-medial granular area (GrPM) medially and by the postero-lateral granular area (GrPL) laterally (Figure 2.3). Preuss and Goldman-Rakic suggested that they correspond to part of area 8Ad and area 45, respectively. This conclusion is based on more than their topological relationships with GrP and area 6. Preuss and Goldman-Rakic pointed out that both the medial and lateral areas in bushbabies and macaque monkeys have smaller pyramidal cells and more prominent horizontally oriented myelin bundles than does area GrP. On similar grounds, they concluded that the

yet more medial areas, called dorsal granular cortex (GrD) and medial granular cortex (GrM) (Figure 2.3) are homologous with dorsal and medial parts of area 8B in macaques, respectively (see Figure 1.2).

With somewhat less confidence, Preuss and Goldman-Rakic suggested homologues for the more rostrally situated parts the granular PF cortex of bushbabies, such as the antero-dorsal granular area (GrAD). They considered two possibilities. One is that GrAD in bushbabies is homologous with the rostral part of area 8Ad in macaques and humans. This suggestion is based on the idea that GrP is homologous with only the caudal part of area 8Ad, leaving its rostral part ‘free’ to be the homologue of GrAD. Alternatively, area GrP might be homologous with a combination of the rostral and caudal parts of area 8Ad in macaques. On this interpretation, area GrAD might be homologous with the postero-lateral PF cortex (area 9/46) in the macaque brain or, because it lacks a strong connection with the posterior parietal cortex, with the polar PF cortex (Preuss 2007a). That issue has not been resolved as yet, but the important point is that Preuss and Goldman-Rakic found no evidence that GrAD corresponds to the mid-lateral PF cortex (area 46), a conclusion that is supported by the weakness of connections between area GrAD and the posterior parietal cortex.

As for the orbital PF cortex, Preuss and Goldman-Rakic suggested that the ventral granular area (GrV) in bushbabies might correspond to macaque area 11 (see Figure 1.2). And, overall, they concluded that bushbabies have approximately the same number of orbital subdivisions as do macaques.

Preuss and Goldman-Rakic could not identify a macaque homologue for the area they called GrAL in bushbabies, the antero-lateral granular area. They therefore suggested that this area evolved in bushbabies after the divergence of strepsirrhines and haplorhines.

As one of their most important points, Preuss and Goldman-Rakic noted that many PF areas in macaque monkeys have less myelin than the bulk of frontal cortex and that no such myelin-poor regions appear to exist in the frontal cortex of bushbabies. A recent study with structural imaging has extended this argument to chimpanzees and humans (Glasser et al. 2011). Along with some arguments based on connectivity, they concluded that bushbabies lack homologues of these myelin-poor areas, which include areas 9, 12/47, and 46, and probably area 10, as well. Unless bushbabies are unusual in this regard, these areas evolved in the haplorhine lineage after its divergence from strepsirrhines, and modern monkeys, apes, and humans have them through inheritance. The areas just mentioned all have a granular cytoarchitecture and little myelin, and they make up the bulk of the PF cortex in modern anthropoids, including humans.

Topology

The term topology refers to the spatial arrangement of cortical structures. Specifically, it refers to the relative locations of cortical areas within the two-dimensional cortical sheet, envisaged as if stretched out in order to unfold its sulci and gyri. Preuss and Goldman-Rakic, for example, used the topological relationship of GrP with the premotor cortex (area 6) to identify it as the homologue of the frontal eye field (FEF) in macaque monkeys. The term topology is rarely used in published discussions of cortical evolution, but

evidence about spatial relationships among structures has always been one of the most important features for assessing homologies. Often enough, adjacent structures provide an important guide as to what some otherwise enigmatic structure might be, and they do so because the basic patterning of the body tends to be among the more conservative features of evolutionary development.

A particularly significant aspect of frontal cortex topology involves its relationship with allocortex. As illustrated in Figure 2.1, some frontal areas lie directly adjacent to the kind of cerebral cortex called allocortex, shown in black in the figure. Allocortex has three layers, in contrast to the more complex laminar structure of most of the cerebral cortex. Typical examples include the hippocampus and piriform cortex.

The agranular parts of the PF cortex lie adjacent to the allocortex. In both rodents and primates, for example, the agranular insular cortex borders the piriform cortex and the anterior olfactory nucleus. Despite being called a ‘nucleus’, the anterior olfactory nucleus is an allocortical structure. Other agranular frontal areas such as the anterior cingulate cortex, the infralimbic cortex, and the prelimbic cortex adjoin smaller, more obscure allocortical areas. Although some authorities have developed elaborate names for the cortical areas near the allocortex, such as juxtalallocortex or proisocortex, we consider them all as variants of neocortex, and we do so mainly on comparative grounds.

The agranular PF areas can thus be recognized not only by their cytoarchitecture, but also by the fact that they are adjacent to allocortex. By contrast, the granular PF cortex does not adjoin the allocortex but instead lies next to agranular PF cortex. So topology agrees with cytoarchitecture in designating the granular PF cortex as something different from the agranular PF cortex. Note that this analysis excludes the premotor areas and motor cortex, which are also agranular.

Corticofugal projections

Our argument is also supported by certain aspects of corticofugal connectivity. For example, what is typically called the orbital prefrontal cortex or the orbitofrontal cortex in rodents sends a direct projection to the striatum. Examining the details of this projection provides some diagnostic features, based on the assumption that homologous parts of frontal cortex project to homologous parts of the striatum.

In rats, the projections from the infralimbic and prelimbic areas terminate mainly in the shell of the nucleus accumbens, a part of the ventral striatum (Brog et al. 1993; Reynolds & Zahm 2005). The striatum has two parts, a ventral striatum consisting of the nucleus accumbens, along with some other structures, and a dorsal striatum comprising the caudate nucleus and the putamen. Area 25 and area 32 in macaque monkeys also project to the shell of the nucleus accumbens (Haber et al. 1995, 2006; Ferry et al. 2000), and this feature supports their homology with the areas called infralimbic and prelimbic cortex, respectively, in rodents.

The granular PF areas in monkeys do not project to the nucleus accumbens at all, let alone to its shell, nor do they project to any other part of the ventral striatum. Instead, they project to part of the dorsal striatum and specifically to the caudate nucleus (Selemon & Goldman-Rakic 1985). Thus, the conclusion from the detailed pattern of corticostratial

terminations agrees with the conclusions from cytoarchitecture and topology. The granular PF cortex has no homologue in rats.

The same pattern applies for the orbital PF cortex. In rats, the orbital PF cortex projects to the ventral striatum or immediately adjacent to it (Berendse et al. 1992). In macaque monkeys, the agranular parts of the orbital PF cortex (including the agranular insular areas) send substantial projections to these parts of the striatum. But granular parts of the primate orbital PF cortex project instead to the dorsal striatum. Like granular PF areas on the lateral surface of the hemisphere, the granular areas on the orbital surface project mainly to the caudate nucleus (Haber et al. 1995, 2006; Ferry et al. 2000; Öngür & Price 2000).

The appearance of new PF areas in primates with their corticostriatal projections has been described by neuroanatomists as a ventral shift (Schilman et al. 2008). The agranular PF cortex in rats projects midway between the dorsal and ventral limits of the striatum. In primates, however, the projection from the homologous regions of agranular PF cortex terminates in the ventral third of the striatum. This ventral shift is consistent with the appearance of more dorsal parts of the striatum to which the new PF areas project.

We note here our differences with those who consider the dorsomedial part of the striatum of rodents to be homologous with the caudate nucleus in monkeys and humans, mainly on topological grounds (Balleine & O'Doherty 2010). In rodents, the internal capsule does not divide the caudate nucleus from the putamen as it does in primates. This makes the assignment of homologies within the dorsal striatum difficult, and one can understand why Balleine and O'Doherty draw the conclusion that they do. However, their view of homologies has little, if any, support from comparative neuroanatomy. A small, ventral part of the primate caudate nucleus could have a homologue in rodents. For the most part, however, the head of the caudate nucleus, like the granular PF areas that project to it, evolved in primates.

In addition, Preuss (1995) has pointed to strong projections from the granular PF cortex to the superior colliculus in primates, compared to weaker corticotectal projections from the agranular PF areas in primates or rodents. We do not adopt this as a major argument, however. Although it applies to the dorsal, medial, ventral, polar, and caudal PF cortex, orbital PF areas do not project appreciably to the superior colliculus (Leichnetz et al. 1981).

Sensory inputs

Additional connections support our argument. Agranular parts of the PF cortex receive relatively direct olfactory, gustatory, and visceral inputs in both rats and monkeys (Ray & Price 1993), as Chapter 4 discusses in more detail. The olfactory inputs come from the piriform cortex; gustatory and visceral sensory inputs arrive in agranular PF cortex via relays in the brainstem and thalamus. These connections support the homology of agranular orbital areas in primates and rodents. The granular parts of the orbital PF cortex lack this characteristic and receive these sensory inputs only indirectly from agranular frontal areas.

Autonomic outputs

The agranular PF cortex in rodents and primates differs from the granular PF cortex of primates in other ways, as well. Outputs from agranular PF cortex influence the

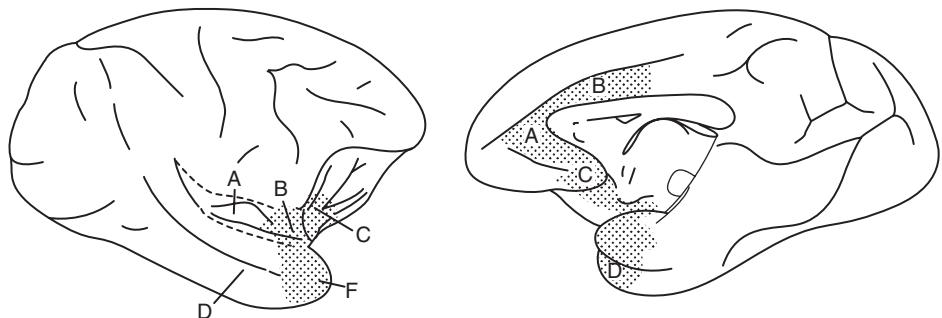


Fig. 2.4 Regions of macaque monkey brains from which electrical stimulation elicits autonomic effects (stippling). Left: lateral view. Rostral is to the right; dorsal is up. Area stimulated: A, granular and dysgranular insular cortex (no effect); B, agranular insular cortex; C, caudal (agranular) orbitofrontal cortex; D, inferior temporal cortex (no effect), F, temporal pole cortex. Right: medial view. Rostral is to the left; dorsal is up. Areas stimulated: A, pregenual cortex (see Chapter 3); B, anterior cingulate cortex; C, subgenual, infralimbic cortex; D, temporal pole cortex. Note that stimulation of agranular areas yield autonomic effects but stimulation of granular areas does not. Reproduced from Kaada BR, Pribram KH, Epstein JA. Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and cingulate gyrus: a preliminary report. *Journal of Neurophysiology* 12:347–56 © 1949 The American Physiological Society, with permission.

autonomic nervous system more directly than those from the granular PF cortex. As shown in Figure 2.4, electrical stimulation elicits autonomic effects from the most caudal part of the orbital PF cortex in monkeys, including the agranular insular areas, as well as from the anterior cingulate, prelimbic, and infralimbic cortex (Kaada 1960). These effects include changes in respiratory rate, blood pressure, pulse rate, pupillary dilation, and piloerection. Stimulation of the granular PF cortex, including granular parts of the orbital PF cortex, has no such effect (Kaada et al. 1949).

Walker's (1940) influential map of the frontal cortex does not recognize that areas 13 and 14 have both granular and agranular parts, but others have noticed that the caudal part of the orbital PF cortex has an agranular cytoarchitecture (Carmichael & Price 1994). Figure 2.1 illustrates this property for areas 14c and 13a, a finding that Mackey and Petrides (2010) have recently confirmed through quantitative cytoarchitectonic analysis (Figure 2.2). Carmichael and Price (1994) included the agranular insular cortex within the orbital group of PF areas, and this addition further reinforces the basic idea.

If the agranular PF areas of other mammals are homologous with the agranular PF cortex in primates, then electrical stimulation of these areas should yield autonomic effects. And, as predicted, this property has been shown for rats, rabbits, cats, dogs, a variety of monkeys, and humans. For example, stimulation of the medial PF cortex induces bradycardia in rabbits (Powell & Ginsberg 2005) and rats (Scopinho et al. 2009). Furthermore, lesions of agranular PF cortex in rabbits (Powell et al. 1997) and rats (Frysztak & Neafsey 1994) disrupt the modulation of autonomic responses by stimuli that predict physiological stressors.

Summary

The distinction between the agranular and granular PF cortex is supported not only by cortical cytoarchitectonics and myeloarchitectonics, but also by the topological relations among areas, the pattern of corticostriatal connections, sensory inputs, and autonomic outputs. So by comparing primates with other mammals we can draw the following conclusions:

1. Nonprimate mammals lack a homologue of the granular PF cortex of primates.
2. Primates and other mammals have several homologous agranular PF areas: the infralimbic, prelimbic, anterior cingulate, agranular orbital, and agranular insular cortex.
3. These agranular PF cortex areas probably evolved in the earliest mammals because all mammals that have been examined to date have homologues of these areas and no homologues are evident in nonmammalian vertebrates.

We can draw a second set of conclusions by comparing the brains of a representative anthropoid primate, such as macaque monkeys, with those of a representative strepsirrhine, such as bushbabies. Figure 2.5 illustrates the relationships among these primate groups, along with certain traits that appeared with the advent of a given lineage, which

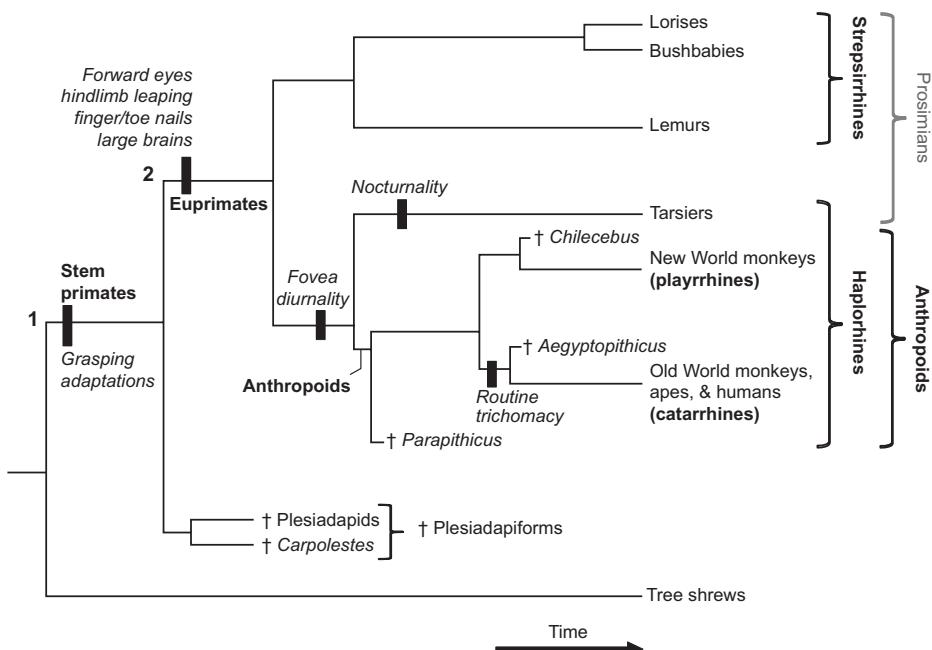


Fig. 2.5 The evolutionary relationships among selected modern and extinct primates. The black bars indicate innovations in selected lineages, with the trait noted near each bar in italics. For groups indicated by brackets to the right, black indicates natural groups (clades), grey indicates other (paraphyletic) groups. †, extinct groups. 1 and 2, differing views of the last common ancestor of primates.

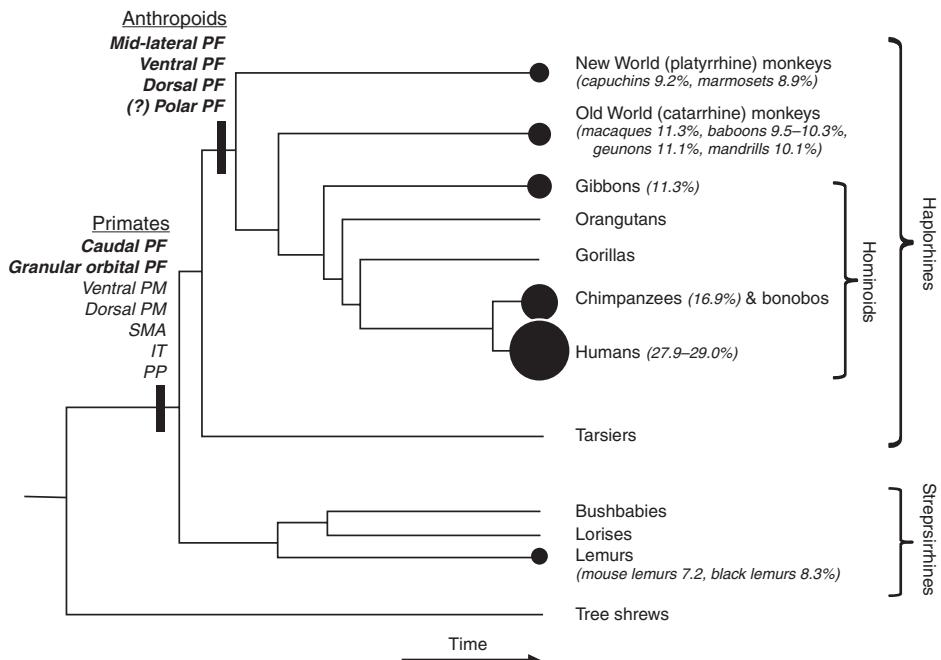


Fig. 2.6 The evolutionary relationships among selected primate species and tree shrews.

Abbreviations: IT, inferior temporal cortex; PF, prefrontal cortex; PM, premotor cortex; PP, posterior parietal cortex; SMA, supplementary motor area. The diameter of each circle at the end of selected lineages is proportional to the estimated proportion of cortex comprising the granular PF cortex, with the percentage for selected species noted to the right of each circle. Format as in Figure 2.5, except that the timescale is linear.

can be found above or below the black bars. Figure 2.6 points out some of the cortical areas that evolved in early primates and in anthropoids.

1. Strepsirrhine primates lack homologues of several areas found in anthropoid primates, including the mid-lateral PF cortex (area 46), the dorsomedial PF cortex (area 9), and the ventral PF cortex (area 12/47). We think that the postero-lateral cortex (area 9/46) and polar PF cortex (area 10) also fall into this category, although the evidence remains less comprehensive on these points.
2. These new areas evolved after the strepsirrhine–haplorhine split, probably in anthropoids, as we later explain.
3. Strepsirrhine and anthropoid primates share two sets of areas. The first set consists of the agranular PF areas that all mammals have; the second corresponds to the granular PF areas that evolved in early primates. The latter set includes the frontal eye field (FEF) and other parts of the caudal PF cortex (area 8), as well as the granular parts of the orbital PF cortex.

Table 2.2 summarizes these conclusions and adds some areas outside PF cortex, including some beyond the frontal lobe. In addition to new PF areas, primates evolved new

areas in the posterior parietal, premotor, and temporal cortex. These developments have been reviewed elsewhere (Kaas 2006, 2012; Preuss 2007b).

Some of the larger uncertainties deserve comment. We use the word probably in relation to area 11, the most rostral part of the orbital PF cortex. Preuss and Goldman-Rakic (1991a) thought that they could identify a homologue of area 11 in bushbabies, although with less confidence than for other areas. Similar issues arise for the postero-lateral PF

Table 2.2 Cortical areas with homologues (+) or possible homologues (?) in mammals, strepsirrhines, and anthropoids

Area	Source	Mammals	Strepsirrhines	Anthropoids
Dorsomedial PF	a			+
Mid-lateral PF	a			+
Ventral PF	a			+
Caudal primary motor	b, c			+
Postero-lateral PF	a		?	+
Polar PF	a		?	+
Caudal PF	a		+	+
Frontal eye field	a, c		+	+
Granular orbital PF	a		+	+
PreSMA	c		+	+
Ventral premotor	c, d		+	+
Dorsal premotor	c, d		+	+
Supplementary motor	c, e		+	+
Cingulate motor	c, e		+	+
Inferior temporal	f		+	+
Posterior parietal	f, g		+	+
Rostral primary motor	b, c	+	+	+
Anterior cingulate	h	+	+	+
Infralimbic	h	+	+	+
Prelimbic	h	+	+	+
Agranular orbital	h	+	+	+
Agranular insular	h	+	+	+
Perirhinal	i	+	+	+

a Preuss and Goldman-Rakic (1991a).

b Rathelot and Strick (2009).

c Wu et al. (2000).

d Preuss et al (1996).

e Preuss (1995).

f Preuss and Goldman-Rakic (1991c).

g Stepniewska et al. (2009).

h Wise (2008).

i Burwell et al. (1995).

cortex (area 9/46) and the polar PF cortex (area 10). If a homologue of the postero-lateral PF cortex exists in bushbabies, then it makes sense to include it in the caudal PF cortex, as we do in Chapter 5. Future work on a diversity of primate species should clarify these issues.

It seems clear that new areas developed in the primate PF cortex during evolution. The idea that other mammals, such as rats, have essentially a replica-in-miniature or amalgam of the primate frontal lobe not only contradicts the comparative evidence, but it also lacks plausibility. The development in primates of a dozen or more new visual areas, along with a number of new posterior parietal and premotor areas, has impressive evidentiary support (Kaas 2006, 2012). The replica-in-miniature theory holds that the PF cortex, more or less alone among the major regions of neocortex, failed to develop new areas during primate evolution. The amalgam theory holds that the small number of PF areas in rats has all of the properties and functions of the primate PF cortex. We can reject both ideas.

Accordingly, we conclude that the granular PF cortex is a primate innovation, both in terms of structure and function. Further support for this idea comes from a recent analysis of gene expression in developing human brains. In a comparison of primate- and rodent-specific genes, Zhang et al. (2011) found that during development the granular PF cortex expressed 198 human- or ape-specific genes, and the authors suggested that these new genes originated in primates to regulate brain growth.

Not only did primates evolve new prefrontal areas, but they developed as part of a suite of primate innovations, which included new premotor, posterior parietal, and temporal areas, along with major parts of the thalamus and striatum that are connected with them (Preuss 2007a, b).

Ventral premotor cortex

If primates developed a suite of new cortical areas, then it would be a mistake to focus solely on the PF cortex. Later we propose that their granular PF areas enabled early primates to adopt a new way of searching for food items and choosing among them in a particular niche. But this development needs to be understood in the context of a new way of seeing, a new way of moving from place to place, and a new way to reaching and feeding. The primate advances in vision and locomotion are straightforward enough, so we mention them only briefly in the following sections. The primate way of reaching and feeding, however, requires more explanation. And so this section focuses on one key area underlying that capacity: the ventral premotor cortex.

Nudo and Masterton (1988, 1990a) found that corticospinal projections originate from three cortical regions in all of the primates that they studied, a sample that included strepsirrhine, platyrhine (New World), and catarrhine (Old World) primates (Table 2.1). They studied bushbabies, slow lorises (*Nycticebus*), squirrel monkeys (*Saimiri*), common marmosets (*Callithrix*), green monkeys (*Cercopithecus aethiops*), and macaque monkeys (*Macaca*). In each primate species, Nudo and Masterton could identify a cluster of corticospinal cells that originated in an area corresponding to the ventral premotor cortex.

They could not find a homologous area in any of 15 nonprimate mammals, even though they examined a reasonable diversity of mammalian species. This comparative evidence indicates that the ventral premotor cortex and its corticospinal projections evolved in early primates.

The ventral premotor cortex contains ~5% of the corticospinal neurons in macaque monkeys (Dum & Strick 2005), and the distribution of their spinal terminations differs from that of most other motor areas. Spinal projections from the ventral premotor cortex terminate mostly in the upper (rostral) segments of the cervical spinal cord, which contain the motor neurons that control neck and shoulder muscles, as well as breathing. Most other motor areas project to nearly all levels of the spinal cord and control the whole body. The ventral premotor cortex also projects to the facial nucleus, a motor nucleus in the brainstem, particularly to those parts controlling muscles of the lower face, lip, and jaw (Morecraft et al. 2001, 2004).

Based on the connections of the various premotor areas, the existence of a ventral premotor cortex has been confirmed in strepsirrhine, platyrhine, and catarrhine primates (Kaas 2004). Bushbabies, capuchin monkeys (*Cebus*) (Dum & Strick 2005), owl monkeys (*Aotus*) (Preuss et al. 1996; Gharabawie et al. 2010), squirrel monkeys (*Saimiri*) (Gharabawie et al. 2010), common marmosets (*Callithrix*) (Burish et al. 2008), and macaque monkeys (Lu et al. 1994) all have a ventral premotor cortex that connects with the primary motor cortex, as well as with the posterior parietal cortex. As with the corticospinal projections, these corticocortical connections indicate that the ventral premotor cortex evolved in early primates.

As we intimated earlier, the importance of this innovation is that it relates to the niche to which the early primates adapted. To preview our discussion of that niche, early primates moved along small branches, using one hand to cling to the branch and the other to reach for food. In descendant primates, such as macaque monkeys, the ventral premotor cortex continues to play a role in reaching and grasping. For example, inactivation of this area impairs the ability of the animals to calibrate the size of their grasp according to the size of the object as they view it (Fogassi et al. 2001).

Summary

The ventral premotor cortex evolved in early primates, a development that accompanied the appearance of the granular PF cortex and new parts of the temporal and posterior parietal cortex. Based on its connections with the spinal cord, the ventral premotor cortex seems to play a role in controlling mouth, head, and reaching movements, rather than movements of the hindlimbs. We take this specialization as a clue that the evolution of these new areas had something to do with forelimb-based foraging. Although they do not project directly to the spinal cord, other premotor areas also have a specialization for forelimb, as opposed to hindlimb, representations. These areas include the preSMA and the rostral part of the dorsal premotor cortex. In the following sections, we reconstruct the niche of early primates and explain how they adapted to it through advances in vision, movement, and reaching.

Early primates

Fossil evidence shows that primate innovations include an opposable thumb or hallux, grasping hands and feet that have nails rather than claws on most digits, and frontally directed eyes (Fleagle 1999; Rose 2006). Primates also have large brains and live long lives. Because of our frontally directed eyes, much of the literature on primate brains has focused on adaptations in the visual system, including the superior colliculus, lateral geniculate nucleus, and several new areas of visual cortex. All of these adaptations have been discussed in considerable detail (Barton 2004; Kaas 2006; Preuss 2007a). On their own, however, these traits tell us little about the granular PF cortex. To understand what advantages the granular PF cortex conferred on early primates, we need to understand how they made a living.

We propose that early primates and their nearest relatives developed a new way of foraging and that it involved the prefrontal cortex. This new way of foraging involved a suite of adaptations for finding, choosing, moving towards, reaching for, and feeding on foods that early primates found in the fine branches of angiosperm trees. Indeed, the close relationship between primates and flowering trees has led some experts to suggest that primates evolved to exploit the adaptive radiation of angiosperms (Sussman 1991).

Foraging in fine branches involved a host of specializations in both body and brain, and we suggest that these ecological factors account for the appearance of the new granular PF areas and their functions. We do not deny that the nature of the social group had an influence on the evolution of the primate brain (Dunbar 2009), but the early primates probably lived relatively solitary lives in dispersed social systems (Muller & Thalmann 2000).

Some idea about the way in which early primates foraged can be inferred from the study by Bloch and Boyer (2002) on *Carpolestes* fossils, a species that lived ~55 million years ago (Ma). Figure 2.5 shows the relationship of these animals to modern primates and Table 2.1 lists some key terms. Two views of early primate evolution have developed. One considers descendants of the species marked by the '1' in Figure 2.5 to be primates; the other views primates (often known as euprimates or 'primates of modern aspect') as the descendants of the lineage labelled with the '2'. We do not need to decide between these views. It is enough to know that *Carpolestes* was a close relative of early primates, if not an early primate per se.

Bloch and Boyer concluded that *Carpolestes* had many features that promoted efficient limb grasping, but lacked some of the traits that characterize modern primates. Most notably, *Carpolestes* lacked frontally directed eyes and a pronounced capacity for leaping. Like tree shrews (*Tupaia*), a close relative (sister group) of primates, *Carpolestes* had laterally directed eyes. As already mentioned, the eyes face forwards in both fossil and modern primates. Bloch and Boyer also concluded that the hind legs and pelvic girdle of *Carpolestes* could not have supported efficient leaping. On this basis, they concluded that a specialized grasping ability evolved before the leaping capacity and the frontally directed eyes that characterize modern primates. Bloch and Boyer also concluded that the grasping specializations of *Carpolestes* allowed them to exploit the fine-branch niche.

The fine-branch niche consists of resources at the margins of angiosperm trees. The smallest, thinnest, and most distal branches have the bulk of the flowers, which contain nutritious nectar. Fruits, nuts, and seeds provide large nutritional benefits, and they occur where the flowers do: in the fine branches. The fine branches also have many of the youngest and most tender leaves, which animals can digest more efficiently than older leaves. Primates prefer young leaves because they have proportionately more protein and less fibre than mature leaves.

Cartmill (1974) and Martin (1990) have also concluded that early primates adapted to the fine-branch niche, but they differ from Bloch and Boyer in stressing adaptations for visually guided movement (Martin 1990) or visually mediated predation on insects (Cartmill 1972; Kirk et al. 2003), rather than the exploitation of fruit, flowers, and nectar (Sussman 1991; Bloch & Boyer 2002). On this view, grasping specializations, frontally directed eyes, and hindlimb-dominated leaping combined as adaptations for foraging in dim light on flimsy branches (Cartmill 1974, 1992; Schmidt 2010). Early primates moved along these branches by leaping and grasping.

As Jenkins (1974) pointed out, many mammalian species exploit the fine-branch niche, with squirrels prominent among them. So if early primates and their predecessors competed for resources in the fine branches of angiosperm trees, they needed an edge. Jenkins proposed that one such advantage involved a life confined to the fine branches rather than one that involved occasional entry into that niche.

A life confined to fine branches presents many challenges. Regardless of what foods they foraged for most—*insects, tender leaves, fruits, nectar, seeds, nuts, or flowers*—early primates had to move among the fine branches to do so, choose effectively among the food items there, and consume them without falling.

In the next sections, we therefore review the visual and motor specializations that primates developed in order to enable them to exploit the fine-branch niche. At the end of this section, we propose that their new granular PF areas helped early primates find and choose among high-value food items that they found in the fine-branch niche. In order to understand this suggestion, we need to appreciate the entire suite of adaptations that led to new ways of seeing, moving, reaching, and feeding. Primates are often called ‘visual animals’. We have not used this vague phrase, but those who do surely do not mean that other animals cannot see. Instead, they intend to emphasize the predominance of vision in primate behaviour. Vision predominates in primates, even where there is no *prima facie* reason that it should do so. Vision predominates in reaching for food (this chapter), vision predominates in finding and attending to foods (Chapter 5), and vision predominates in learning about which foods to choose (Chapter 4). It is only by understanding the entire set of adaptations to the fine-branch niche that one can fully appreciate the advantages that the granular PF cortex brings.

The primate way of seeing

Comparative neuroscientists have emphasized the visual advances of primates, and for good reason. These changes must have provided a key selective advantage. However, understanding their contribution to the origin of the granular PF cortex requires us to

recognize how vision in early primates differed from that of many modern primates, including humans.

Our intuitions about vision come from our experience, which consists mainly of foveal vision in bright light. So it is natural to assume early primate vision depended on focal, high-acuity, bright-light, fovea-dependent colour vision. But vision in early primates had none of these properties. Early primates lacked a fovea and foraged at night, in dim light (Rose 2006). Because they lacked a fovea, the development of frontally directed eyes and large binocular visual fields could not have had anything to do with the kind of foveal vision that humans and other modern primates have. Instead, the frontally directed eyes of early primates must have evolved for vision in dim light, without either the high acuity mediated by the fovea or the kind of colour vision that humans (and other Old World primates) have.

The large binocular fields generated by more frontally directed eyes would have produced a larger visual field for stereopsis and depth perception. Barton (1998) showed that brain size and the size of the visual cortex correlate with the degree of frontal eye orientation in modern primates, and he attributed these traits to the importance of binocular vision, and especially an increased stereoptic field. Stereopsis is of obvious importance in leaping and reaching for food in the fine-branch niche (Cartmill 1974; Martin 1990).

But binocular vision has advantages beyond stereopsis. It could promote sensitivity in dim-light conditions by summation of inputs from the two eyes onto cortical neurons (Hughes 1977; Allman 2000), and it permits at least one eye to see distant objects around the obstructions encountered in the cluttered, leafy environment of the fine-branch niche (Changizi 2009). Frontally oriented eyes also provide animals with increased visibility and depth perception below and in front of their heads, which could be important in reaching for and manipulating objects in that part of space (Barton 2004). As Barton pointed out, animals with laterally directed eyes have a problem. The orbital skull bones constrain their ability to verge the eyes toward close objects, and this would be particularly true for objects in the lower visual field, beneath their head, where manipulation occurs. The frontally directed eyes of early primates probably helped them to overcome this problem.

Thus the frontally directed eyes of early primates may have aided the identification and acquisition of foods in several ways, including increased sensitivity in dim light, better lines of sight around obstacles, enhanced vision beneath the head, and improved depth perception.

The primate way of moving

Primates also have a different method of locomotion compared to other mammals, and this, too, reflects a life restricted to the fine-branch niche. A number of adaptations were required to cope with the difficulties encountered in moving through and foraging in an arbour of thin, flexible branches.

Life in and among fine branches led to changes in gait. For arboreal locomotion in the fine-branch niche, primates use a different pattern of muscle recruitment compared to other mammals (Larson 1998). Key differences include less push-off force from both the

hindlimbs and the forelimbs along with less stiffness of the forelimbs (Schmidt 2010). The low forces used by primates limit the oscillations that their movement produces in the branches, which could otherwise attract predators.

Most notably, early primates used their hindlimbs for the driving force of locomotion to a greater extent than their nonprimate ancestors. A hindlimb-dominated form of locomotion freed the forelimbs for other functions, including stability, steering, grasping, and manipulation (Schmidt 2010). It also enabled hand-to-mouth feeding, with one hand providing stability and the other reaching for food and bringing it to the mouth (MacNeilage et al. 1987). This new way of reaching and feeding involved both the new premotor areas and the new granular PF cortex that appeared in early primates. We take up the ventral premotor cortex first.

The primate way of reaching and feeding

To understand the importance of the ventral premotor cortex, and why early primates required new areas with new functions, we need to recognize that feeding in the fine-branch niche is no picnic. On a picnic, both forager and food can remain stationary. Feeding in a fine-branch niche presents a much more serious challenge. Early primates had to master body stabilization on a flimsy platform while reaching to foods that moved relative to their bodies. Even after they had grasped the foods that they wanted to eat, these animals faced serious problems in bringing food to their mouth while maintaining their balance on a thin, flexible branch.

The ventral premotor cortex and its projections to the brainstem and spinal cord probably contributed to solving these problems of arboreal life. Nudo and Masterton (1990b) searched for correlations between the area's corticospinal projections and various aspects of motor behaviour, including manual dexterity and hand–eye coordination. They found little correlation with these factors. Instead they found that the relative extent of the ventral premotor area correlated significantly with an arboreal life. This correlation does not tell us how the ventral premotor cortex contributed to that life, but a role in reaching and hand-to-mouth feeding seems likely.

As we noted earlier, the corticospinal and brainstem projections from ventral premotor cortex terminate on motor neurons that control muscles of the head, shoulder, lower jaw, and lip. They do not terminate on the motor pools that control muscles of the lower trunk and hindlimbs. These features suggest that the ventral premotor cortex plays a larger role in forelimb, head, and mouth movements than in the hindlimb-dominated locomotion of primates. Forelimb, head, and mouth movements combine in hand-to-mouth feeding. Moving the hand toward the mouth to feed requires the coordinated orientation of the hand, head, and mouth, and the ventral premotor cortex could provide this control (Preuss 2003).

Evidence from electrical stimulation of the cortex also suggests that the ventral premotor cortex plays a role in hand-to-mouth feeding. In macaque monkeys, Graziano et al. (2002) electrically stimulated the ventral premotor cortex for periods of several seconds. This stimulation evoked the closure of the hand together with a movement of the hand to the mouth. It also evoked the opening of the mouth and movement of the head so that it

rotated the mouth toward the hand's location as it approached the mouth. So, in essence, cortical stimulation artificially evoked feeding behaviour. Similar effects have been evoked from the posterior parietal cortex and premotor areas in other primates (Stepniewska et al. 2009; Gharbawie et al. 2010).

Along with solving the problem of bringing food to the mouth while perched on a flimsy, oscillating substrate, reaching to food in the fine-branch niche also requires postural stabilization. MacNeilage et al. (1987) noted that modern strepsirrhines hunt insects with a unimanual predation technique, one that makes use of postural support with one hand while reaching toward the food and bringing it to the mouth with the other.

One motor control strategy to accomplish this feat is to keep the shoulder at a fixed location regardless of the swaying of tree limbs. The projection of the ventral premotor cortex to the muscles that control the shoulder girdle could compensate for unintended body movements resulting from instability of the substrate.

The other strategy involves continuously calculating the difference between the current position of the hand and the food item. In this way, motor commands will adjust automatically as the movement approaches a food object, even as the body sways and the food items move because of wind or the influence of the animal on the branch. Wise (2007) summarizes the evidence for these conclusions.

Taken together, the neurophysiological and psychophysical evidence indicates that primates have evolved a unique way of reaching. Shadmehr and Wise (2005) lay out the case for this conclusion at book length, but we present some of their key findings here:

1. Primate reaching occurs within a visual frame of reference (see Figure 5.3). Some cells encode the location of a target in retinal coordinates, and others encode hand position in the same coordinate frame. *Prima facie*, the motor control system only requires the spatial relationship between the hand and the target. This information, alone, specifies the joint-angle changes and forces that will bring the hand to the target. In other terms, reaching seems to require only body-centred coordinates, also known as an egocentric or intrinsic frame of reference (Chapter 3). The primate brain does not need encode reaching movements in a retinal reference frame, but the evidence indicates that it does so. For example, cell activity in the ventral premotor cortex better reflects movement trajectories in extrinsic retinal coordinates than in intrinsic motor coordinates.
2. The fact that primates compute reach targets and current hand position in a retinal coordinate frame makes it necessary to recalculate their motor plans every time that their eyes move. Again, no *prima facie* reason exists for such recalculations. When the eyes change their orientation, but the reach target and hand remain stationary, the motor command does not need to change. Yet the primate brain recalculates target location, hand location, and motor plans every time the eyes move and in anticipation of the eyes moving.
3. Experiments in human subjects show that the primate brain computes reaching movements in a visual frame of reference, even for acoustic targets. People slightly overshoot a target if it lies in their peripheral visual field. For visual targets this makes

sense because peripheral vision has some inherent inaccuracies. The same inaccuracy in reaching occurs for acoustic targets, however, although there is no need to bring retinal properties into the computation.

- Congenitally blind people make straighter, better ‘visually guided movements’ than do sighted people, a phenomenon that results from the small visual distortions that sighted people experience.

These findings demonstrate the dominance of vision in the primate way of reaching. In early primates, their newly evolved premotor and posterior parietal areas performed the computations for reaching movements in a retinal reference frame, as the homologues of these areas do in their descendants. Later we argue that vision also dominates the search for and choice of food items and that newly evolved PF areas support these functions.

Given that the ventral premotor cortex generates a reach command in order to achieve a goal, it should come as little surprise that it has cells, called mirror neurons, that encode goal achievement independent of who or what achieves that goal (Umiltà et al. 2001). The ventral premotor cortex also plays a role in coordinating head and hand movements. In performing these functions, the ventral premotor cortex contributes to solving two of the problems that early primates encountered as they foraged in the fine-branch niche: reaching to food items and bringing them to the mouth.

The primate way of searching and choosing

Adaptive success in the fine-branch niche required more than improvements in visually guided leaping, reaching, and grasping. We suggest that the predominance of vision also promoted advances in the way that early primates searched for food and in the way that they evaluated the desirability of what they found in the cluttered environment of the fine-branch niche. Earlier we said that certain parts of the granular PF cortex evolved in early primates. Here we propose that these new granular PF areas mediated search and valuation functions in early primates and continue to perform these functions in modern primates.

Based on the evidence from bushbabies that we summarized the first part of this chapter, we accepted Preuss’s conclusion that early primates had homologues of two granular PF areas: the caudal PF cortex (area 8), which includes the FEF, and the granular parts of the orbital PF cortex (the granular OFC), which includes area 11 and rostral parts of areas 13 and 14.

Both of these areas receive strong visual inputs. The FEF has extensive connections with early (low-order) visual areas, such as V2 and V3 (Stanton et al. 1995), for example, and the granular OFC has sizable connections with the inferior temporal cortex and the perirhinal cortex (Saleem et al. 2008).

Chapter 5 proposes that the caudal PF cortex provides a mechanism for searching for food items and visual signs of food. It also plays a role in attending to those items, and this function includes both covert attention and overt attention (eye movements). Chapter 4 proposes that the granular OFC encodes the current value of a food item and links previous foraging choices to the outcomes that follow each choice, including the visual features of outcomes such as specific foods and fluids. High value objects thus become the targets of reaching, grasping, manipulation, and feeding movements.

Summary

Early primates evolved to exploit a fine-branch, nocturnal foraging niche in angiosperm trees. Their frontally directed eyes lacked a fovea or full-colour (trichromatic) vision, but large binocular fields of view allowed them to function well in a dim, cluttered environment, to calculate distances with depth perception, and to bring both eyes to bear on a region below their head where they could manipulate objects. With their forelimbs freed by a new primate way of locomotion, early primates could reach for food items in a visual frame of reference and bring them to their mouths without falling. To exploit their visual advances, new posterior parietal and premotor areas evolved to control the primate way of reaching.

In addition to the advances just mentioned, however, early primates needed to search for desirable food objects in the fine-branch niche and assess their current biological value. Their new granular PF areas provided early primates with advantages in performing these functions, as their homologues do in the descendants of these animals today.

Anthropoid PF cortex

So far we have focused on the evolution of early primates, which developed the first granular PF areas. Later primate evolution produced the **anthropoids**, and some of these primates evolved additional parts of the granular PF cortex.

As explained earlier, a comparison of PF areas in a representative strepsirrhine primate (a bushbaby) with a representative anthropoid monkey (a macaque) led Preuss and Goldman-Rakic (1991a) to conclude that several new PF areas evolved in anthropoids. In our terminology (see Figure 1.4), these new areas include the mid-lateral PF cortex (area 46), the dorsomedial PF cortex (area 9), the ventral PF cortex (area 12/47), and probably the polar PF cortex (area 10). The next part of this chapter explores when these new areas appeared and the selective pressures that might have led to their development.

Figure 2.5 illustrates the relations among many living primates, together with some extinct primates known only from fossils, and Table 2.1 lists some key terms. Kay et al. (2004) date the split between the haplorhines and strepsirrhines at no less than 55 Ma. They estimate that the split between anthropoid primates and tarsiers occurred at ~45 Ma and that between the catarrhines (Old World primates) and platyrhines (New World monkeys) at ~34 Ma. To put these values in perspective, primates first appeared ~65 Ma, apes and other catarrhine (Old World) primates went their separate ways ~23 Ma, and the human and chimpanzee lineages diverged ~7 Ma.

Comparative evidence, explained in the next section, indicates that early haplorhines shifted from the nocturnal foraging habit practised by their immediate ancestors to a diurnal life. They also developed a more frontal orientation of their eyes and a true fovea, which led to improved visual acuity. Much later, after the divergence of platyrhine (New World) and catarrhine (Old World) anthropoids, the catarrhines evolved the three-colour (trichromatic) vision found in humans (deValois & Jacobs 1998; Williams et al. 2010). This *routine* form of trichromatic vision differs from the polymorphic kind of trichromacy that occurs in platyrhines, a topic we return to later.

Many accounts of cortical evolution in anthropoids have placed well-deserved emphasis on a proliferation of visual areas (Kaas 2006), with the PF cortex receiving much less attention. Yet a large frontal lobe is as prominent a characteristic of modern anthropoids as their large visual cortex, frontally directed eyes, and fovea. As we argue later, their large frontal lobe largely reflects a large granular PF cortex.

Ecological factors

Changes in the PF cortex came about because the shift to daytime activity had profound consequences beyond vision. It affected the size, way of moving, diet, and niche of anthropoid primates. Anthropoids became larger over time, adapted the original primate way of moving to become arboreal quadrupeds, and came to depend on products of angiosperm trees beyond those of the fine-branch niche. The early anthropoids and their descendants faced new competitors and a markedly increased risk of predation that came with diurnal life, as well as the competition that came from each other.

Perhaps most importantly for the granular PF cortex, as anthropoids evolved they also contended with a marked volatility in the foods that they came to require, which have intermittent periods of scarcity even in the lush tropical environments in which anthropoids evolved and most still live (Oates 1987).

Social factors

A shift to diurnal foraging increased the risk of predation and anthropoids probably adapted to predation, in part, by living in groups. Among other advantages, it is useful to have many eyes to look out for predators. As a result of these new social structures, anthropoids would have had to make choices involving interactions with other group members, and not just about foraging. These factors would also have had consequences for the evolution of their brain, in general, and their PF cortex in particular (Dunbar 2009).

Some recent evidence points to parts of the newly evolved granular PF areas, along with other parts of PF, as playing a role in social choices. Recent findings indicate that the mid-lateral PF cortex increases in size as monkeys interact in progressively larger social groups (Sallet et al. 2011).

An area within the superior temporal sulcus also increases in size as social groups enlarge. Cells in this area respond to the gaze angles and facial orientation of primates (Perrett et al. 1985), as well as to their observed movements (Jellema & Perrett 2003). This finding is relevant to the PF cortex because this superior temporal area projects to the anterior cingulate cortex, a part of the medial PF cortex (Chapter 3). And, in accord with this projection, the larger the social group, the greater the covariance between activation in the superior temporal area and activation in the anterior cingulate cortex (Sallet et al. 2011). This finding is of interest for two reasons. First, Yoshida et al. (2011) reported cells in the medial PF cortex with activity that distinguishes self from others; these cells encode the actions of another agent in a social context. Second, Rudebeck et al. (2006a) found that monkeys with lesions of the anterior cingulate gyrus no longer show an interest in pictures of other monkeys, even when they depict a monkey staring at them in a threatening way. Chapter 9 picks up this discussion with regard to the human brain.

Summary

Anthropoids inherited diurnal foraging from their haplorhine ancestors and became larger over time. The comparative evidence shows that as they did so they evolved new PF areas. In the next section, we review evidence that during their evolution anthropoids came to depend on volatile resources. They became sizable animals, without a capacity to cache food reserves, and they foraged in larger social groups. As such, poor foraging choices cost them time and energy that they could ill afford, especially during periods of dearth. Considering the risk of predation and the competition for scarce foods, anthropoid primates evolved to forage more effectively than their ancestors could. We argue later that their new granular PF areas contributed to reducing the number of risky or unproductive foraging choices.

Ancestral and advanced anthropoids

The brains of the early anthropoids had small frontal lobes, as far as we can tell from fossil endocasts, which show brain structure from impressions formed on the inner surface of the skull (Radinsky 1975, 1979). By studying the endocasts of extinct primate species, Radinsky found that for a long period during anthropoid evolution these animals had small frontal lobes. Figure 2.7A depicts the fossil endocast of one extinct anthropoid, *Aegyptopithecus*, an early catarrhine primate that lived ~33 Ma (Kay et al. 2004). *Aegyptopithecus* had a conspicuous central sulcus but little of the frontal cortex that we would expect of modern anthropoids. Based on this evidence, Radinsky concluded that the expansion of frontal lobes occurred after the expansion of visual areas in anthropoids. According to his analysis, expansion of visual cortex began in the earliest phase of primate evolution, beginning ~55 Ma. By the time of *Aegyptopithecus*, that expansion had reached the modern anthropoid range, but the frontal lobes remained relatively small.

Fossils also indicate the size of the *Aegyptopithecus* brain, as a whole. Modern anthropoid brains exceed the size expected for a strepsirrhine primate of their body size. Allman (2000) and Streidter (2005), among others, have emphasized this anthropoid trait, often referred to as an ‘upward grade shift’ in brain size. Figure 2.7 illustrates this upward shift for modern primates. It also shows the brain to body relation in *Aegyptopithecus* (point A in Figure 2.7D). These relatively early catarrhines had small brains for their body size, within the range of modern strepsirrhine primates.

Figure 2.7D also plots the brain-size to body-size relationship of another extinct anthropoid, *Parapithecus* (Bush et al. 2004), a primate close to the earliest anthropoids (Simons 2004). Like *Aegyptopithecus*, *Parapithecus* (point P in Figure 2.7D) had a brain in the strepsirrhine range, as did two early platyrhines, *Chilecebus* (point C in Figure 2.7D) (Sears et al. 2008) and *Homunculus* (Kay et al. 2006).

The fact that tarsier brains (point T in Figure 2.7D) also fall within the strepsirrhine range gives further credence to the distinction between a smaller ‘prosimian’ grade of brain size and a larger anthropoid grade. Given their relatively small brains, the fossil evidence from early catarrhines and early platyrhines indicates that brain expansion proceeded independently in Old World and New World primates. The anthropoid brain

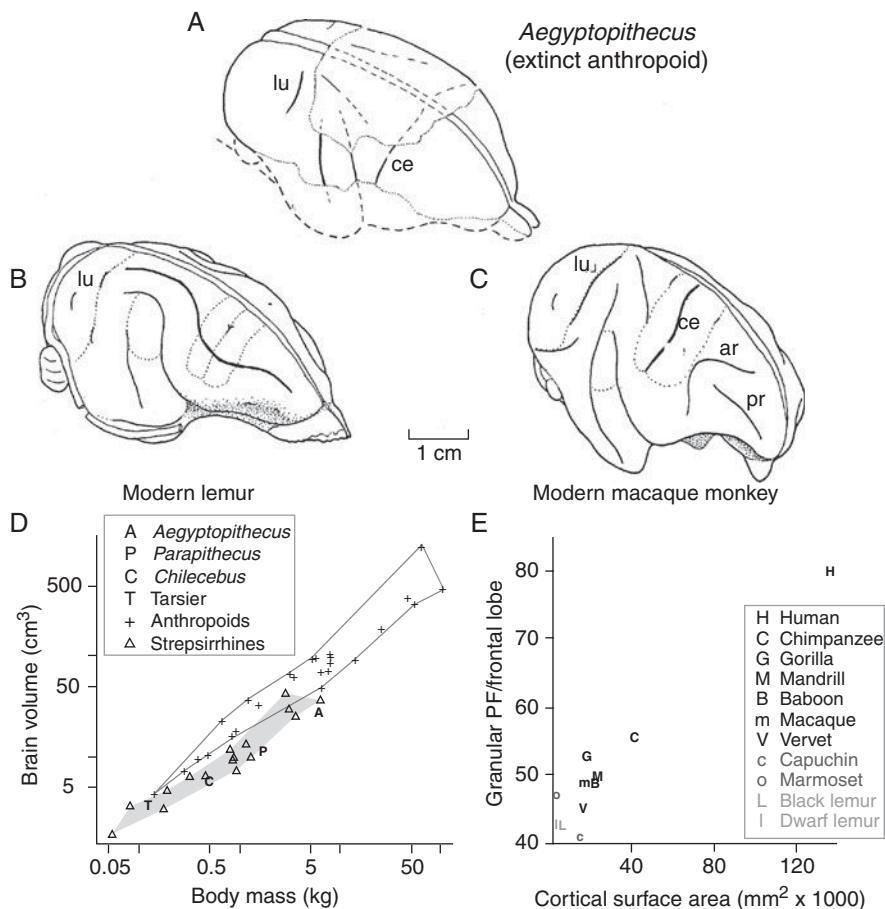


Fig. 2.7 (A-C) Fossil endocast of an extinct anthropoid primate, *Aegyptopithecus* (A), compared to a modern strepsirrhine primate, a lemur (B), and a modern anthropoid primate, a macaque monkey (C). Rostral is to the right and dorsal is up. Abbreviations: ar, arcuate sulcus; ce, central sulcus; lu, lunate sulcus; pr, principal sulcus. The dotted lines in (B) and (C) indicate the approximate locations of, from caudal to rostral: the primary visual, primary auditory, primary somatosensory, and primary motor areas. (D) Brain size versus body size in a selected extinct and modern primates. Abbreviations: A, *Aegyptopithecus*; C, *Chilecebus*; P, *Parapithecus*; T, tarsier. (E) Percentage of the frontal lobes consisting of granular prefrontal cortex as a function of the size of the cortex (surface area). (A-C) Reproduced from Radinsky L. 1975. Primate brain evolution. *American Scientist* 63:656–63. (D) Modified from Bush EC, Simons EL, Allman JM. High-resolution computed tomography study of the cranium of a fossil anthropoid primate, *Parapithecus grangeri*: New insights into the evolutionary history of primate sensory systems. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology* 281a:1083–7, © 2004, John Wiley and Sons, with permission. (E) Modified from Elston GN, Benavides-Piccione R, Elston A, Zietsch B, Defelipe J, Manger P, Casagrande V, Kaas JH. Specializations of the granular prefrontal cortex of primates: implications for cognitive processing. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology* 288a:26–35, © 2006, John Wiley and Sons, with permission.

thus probably remained at the prosimian grade until after the platyrhine–catarrhine split occurred ~34 Ma.

In the remainder of this book, we will refer to species that have attained this upward grade shift in brain size as *advanced* anthropoids solely in order to distinguish the larger, descendant species from the earlier, small-brained anthropoids. Note that, in biology, the word advanced implies only some divergence from the ancestral condition, much as primitive implies only a close resemblance to the ancestral condition. These terms imply nothing about relative capacity or complexity. Furthermore, because most of what we know about the anthropoid PF cortex comes from studies of catarrhines, and of these species mainly macaque monkeys and humans, some of the features that we attribute to advanced anthropoids might represent catarrhine specializations.

Given that the expansion of visual cortex had reached the range of modern anthropoids by the time of *Aegyptopithecus* (Radinsky 1975), which had a brain in the strepsirrhine size range, the relatively recent expansion of the frontal lobe seems to be the biggest factor in brain growth in modern anthropoids. And, like the expansion of the brain in general, this frontal expansion seems to have occurred independently in catarrhines and platyrhines (Williams et al. 2010). Thus the disproportionately *frontal* expansion probably produced the characteristically large brains of anthropoid primates.

Fossil endocasts cannot distinguish the granular from the agranular frontal cortex, but cytoarchitectonic analysis in modern primates can. Brodmann (1912) measured the size of the granular PF cortex in modern primates and showed that the larger the primate brain, the greater the proportion of the neocortex composed by the granular PF cortex. Figure 2.7E shows the relative size of the PF cortex as a proportion of the neocortex in a selection of living primates. In representative anthropoid monkeys, the granular PF cortex makes up 9–11% of the neocortex and 43–50% of the frontal lobe (Elston et al. 2006). The corresponding values for representative strepsirrhines are 7–8% and 41–43%. Unlike the granular PF cortex, the temporal cortex does not become proportionately greater in larger brains (Rilling & Seligman 2002). Thus, as the neocortex expanded in primate evolution, the granular PF cortex seems to have expanded proportionately more than other parts of the cerebral cortex. And, as explained earlier, the evidence from comparative anatomy indicates that this increase involved the development of new areas within the PF cortex. We cannot, of course, rule out the expansion of other parts of the anthropoid frontal lobe, as well.

The conclusion that the expansion of the PF cortex had not yet occurred in early anthropoids, or even in the earliest catarrhines, has an important implication. It means that the selective pressures leading to the origin of anthropoids probably differed from those that led to the appearance of new granular PF areas in later anthropoids. To understand these later selective factors, we need to consider the key anthropoid innovations in more detail.

Diurnal life and the fovea

Early haplorhines shifted to diurnal activity and evolved the primate fovea, and early anthropoids inherited both features. The eyes also adopted a more frontal orientation in

early anthropoids, and an orbital bone developed behind the eye to serve as a wall between the muscles of the jaw and the eye.

A diurnal origin of anthropoids gains support from both comparative and fossil evidence. Small eyes require less light than large ones, and all early anthropoid skulls have relatively small orbits, a strong indication of diurnal life (Fleagle 1999). Comparative evidence shows that nearly all modern anthropoids have a pattern of daytime activity, but few other primates do (Heesy & Ross 2004). Early anthropoids inherited diurnal life and most have retained it.

The evidence for a haplorhine origin of the fovea depends entirely on comparative evidence. Tarsiers and anthropoid primates all have a fovea characterized by many common features. The fovea measures ~0.7 mm in diameter and has about 250,000 cone-shaped photoreceptors per square millimetre. It develops within a larger retinal specialization called the macula. In all haplorhines, the fovea lacks blood vessels, rod-shaped photoreceptors, and retinal ganglion cells. Even within the fovea, photoreceptors have a steep density gradient, with the highest cone densities in its centre. In strepsirrhines, by contrast, tiny rods dominate the central retina (Bumstead O'Brien 2008).

A fovea evolved independently many times in vertebrates, probably three times in teleost fishes, three times in reptiles, separately in early birds, and once in primate history (Ross 2004). The haplorhine fovea is unique among mammals, which means, of course, that other (strepsirrhine) primates also lack a fovea. Some mammals, such as carnivores (including cats and dogs), have evolved retinal specializations that resemble the haplorhine fovea in some respects. Cats, for example, have a visual streak consisting of a broad, horizontally oriented concentration of photoreceptors near the centre of the retina. The visual streak lacks the high concentration of cone receptors and most of the other defining characteristics of the haplorhine fovea (Hughes 1977). The visual streak almost certainly evolved independently.

The more frontal orientation of anthropoid eyes accentuated a trait that evolved in early primates. Combined with the evolution of the fovea, the enhanced acuity and stereopsis in the central field of vision represented an important visual advance. Accordingly, as mentioned earlier, the degree of frontal eye orientation correlates with both brain size and the size of the visual cortex (Barton 1998), which as we have seen comes along with an increased number of visual areas (Kaas 2006). It also correlates with the size of the visual processing channel that deals with high-acuity vision (Barton 2004). As with primates generally, these anthropoid advances enabled improvements in visually guided reaching toward and manipulation of objects.

Later in anthropoid evolution, catarrhine (Old World) primates developed the kind of colour vision that humans have inherited. As already mentioned, this kind of colour vision is called *routine trichromacy* to distinguish it from a different (polymorphic) kind of trichromacy seen in many platyrhine (New World) monkeys—although one group of platyrhines, howler monkeys (*Alouatta*), evolved routine trichromacy independently.

Colour perception depends on the contrasts among signals emanating from cone-shaped photoreceptors tuned to particular wavelengths of light. The mechanism of such contrasts is called colour opponency. Most mammals, including strepsirrhine primates,

have only two kinds of cone receptors: one responds best to short-wavelength light, and the other responds best to long-wavelength light. In catarrhine primates, the gene for the long-wavelength type of cone photoreceptor duplicated and diversified into two kinds of cones, with a small difference in their peak sensitivities. As a result, colour vision in catarrhines has an additional dimension compared to the ancestral, dichromatic condition. In platyrhine monkeys, only females have three kinds of cones, which arise through a different and independently evolved process. They use gene polymorphisms to achieve trichromacy rather than two separate genes.

Improved visual acuity, better depth perception, and improved colour vision provide obvious advantages for daytime foraging. Indeed, foraging in bright light leads to improvements in foraging and communication even without a fovea. And even without trichromatic vision, the fovea gave anthropoids a sophisticated, in-depth view of objects.

The daily life of one anthropoid species illustrates the importance of the fovea. Struhsaker (1980) reported field studies of the red-tail monkey (*Cercopithecus ascanius*), a catarrhine monkey. He found that they spend 21% of each day scanning their visual world, presumably for fruits, insects, and predators. They spend an additional 17% of the day travelling from place to place to obtain resources, based presumably on what they have seen. Once they reach a fruitful location, their feeding time takes up 34% of their day. Taken together, the time spent looking around and acting on what they see amounts to more than 70% of their active time. Of the remaining hours, these monkeys spend 10% resting and 5% engaged in social interactions, such as grooming. The proportions will vary from species to species, but red-tail monkeys seem representative enough to make the point: with a new mechanism to gain better information at a distance, anthropoid primates look around a lot.

But the development of a fovea, improved depth perception, and diurnal life were unlikely, by themselves, to have spurred the development of the new granular PF areas that appeared in advanced anthropoids. Most of the visual developments occurred before the frontal lobe expanded in these animals. As explained earlier, the expansion of the frontal lobes occurred after the split between catarrhines and platyrhines, but the fovea and more frontally oriented eyes appeared before the origin of anthropoids, in early haplorhines. Instead of directly driving a frontal expansion, the fovea, improved depth perception, and diurnal foraging probably drove the well-documented changes in the visual cortex, including its expansion and the appearance of the many new visual areas (Kaas 2006, 2012). The later development, in catarrhines, of routine trichromacy, accentuated these developments.

Among the visual specializations of anthropoids, only trichromacy occurred sufficiently recently to account for the expansion of the anthropoid brain and the PF cortex. As we have just mentioned, routine trichromacy first appeared in early catarrhines. We cannot rule out trichromacy as a driving force for granular PF cortex expansion, but we doubt it. The expansion of the granular PF cortex needs to be placed in the context of the overall expansion of the cortex, with the new PF areas taking their place along with other new or expanded areas.

For example, Rathelot and Strick (2009) found that the caudal part of the primary motor cortex (area 4) has the bulk of direct monosynaptic projections to spinal motor

neurons, and Kaas (2004) concluded that the appearance of two divisions of the primary motor cortex probably occurred in anthropoids. The caudal region seems to be a new area in anthropoids, in the sense explained earlier. Because it receives cutaneous inputs (Strick & Preston 1978; Tanji & Wise 1981), we think that it probably plays a role in the manipulation of objects. Importantly, this capacity could be especially important in fruit selection. A particular type of somatosensory receptor, called Meissner corpuscles, concentrates in the epidermal ridges of the fingertips and other glabrous surfaces. These highly sensitive receptors respond to skin deformation with a rapidly adapting response, which means that they signal small forces applied to the skin surface and changes in those forces. A comparison of nine anthropoid species showed that the density of Meissner corpuscles in a species correlates with the extent of its fruit consumption. This relationship probably reflects a variable ability to use hardness and softness to assess the ripeness of fruits, as probed by palpation and manipulation (Hoffmann et al. 2004). Cutaneous input to the primary motor cortex has little relation to trichromacy, but it can be understood as playing a comparable role in some ways. The concentrated touch receptors on the anthropoid hand have been called a tactile ‘fovea’ in recognition of this idea.

Therefore the expansion of the PF cortex and the addition of new granular PF areas should be viewed in the context of a more general brain expansion, one that involved new or expanded areas in many parts of the cerebral cortex. Trichromacy, high-acuity foveal vision, and enhanced depth perception enabled anthropoids to exploit the benefits of diurnal life for foraging and communication; but by themselves they seem unlikely to account for the appearance of the large number of new areas within the granular PF cortex. Something more than vision drove the frontal expansion in advanced anthropoids.

It takes an expert to make all of the distinctions that are possible once high-acuity, trichromatic vision evolved, and this expertise arises from perceptual learning. Monkeys become very proficient in fine discriminations between very similar colours as they gain experience in trying to make such distinctions (Gaffan 1996), and it seems likely that the expansion of the inferior temporal cortex results in part from the demands for fine discrimination between colours, visual texture, and so forth. Lesions of inferior temporal cortex in macaque monkeys cause a severe impairment in detecting differences between hues that have a high degree of similarity (Huxlin et al. 2000). In the same way, the expansion of the inferior temporal cortex also reflects the demand for high-acuity central vision. Lesions of the inferior temporal cortex cause an impairment in highly localized central vision, as opposed to discriminations that take in a larger field of vision (Horel 1994). As Chapter 7 explains, these inferior temporal areas provide a major input to the granular PF cortex.

To help us understand the selective pressures that led to new areas within the anthropoid PF cortex, we look to the costs of diurnal life rather than its benefits. Diurnal life has several advantages, as explained earlier. Daytime foraging improves the ability to use distant visual cues to detect and evaluate resources, identify potential predators, and engage in social communication. However, these benefits come with several costs: an increased risk of predation, greater competition, and heat stress.

Daylight foraging puts the animal at substantially increased risk of predation, so anthropoids need to search for predators during and between bouts of foraging. The development of the fovea presumably helped detect predators, but the risk remained much greater than for their nocturnal ancestors.

Daytime activity also increases the competition for food with other diurnal animals, some of which must, at first, have been better adapted to diurnal life. Anthropoid primates compete with fruit bats, squirrels, frugivorous birds, and in some places with marsupials, as well (Oates 1987). Birds, after all, can fly directly to their food, and primates cannot. Additional competition comes from members of the same social group, and all forms of competition become more important during periods of scarcity. Such competition is accentuated because diurnal species typically have larger social groups than nocturnal ones, as mentioned earlier, presumably as protection against predation.

Diurnal foraging also increases susceptibility to heat stress, a problem avoided by nocturnal foragers. Afternoon temperatures in the tropics, where most primates live, usually rise to 30–35°C or higher, and the ability to regulate internal temperature begins to deteriorate with a heat load of that magnitude. For a substantial part of the day, tropical heat makes foraging dangerous, and most anthropoids forage soon after awakening in the morning and just before their nightly rest period (Oates 1987). So heat stress limits the amount of time available for foraging, even with the long and regular days of the tropics.

Time restrictions must have exacerbated the competition for scarce food resources, and the risk of predation complicated all foraging choices. We suggest that these problems selected for the ability to improve foraging choices and to learn how to do so quickly. In Chapter 8, we argue that the phylogenetically older trial-and-error learning mechanism produced too many poor choices and that new parts of the granular PF cortex implemented a learning mechanism that improved foraging choices. As a result, advanced anthropoids could compete for scarce resources more effectively than their ancestors could.

To understand how the new parts of the granular PF cortex could provide this advantage, we need to know how advanced anthropoids foraged, why crucial resources became scarce from time to time, and why poor foraging choices cost so much.

Size, diet, and the anthropoid way of moving

Like other animals, anthropoids need to seek and consume energy-laden foods, including proteins and their amino acids, various minerals, vitamins, fluids, and other nutrients, such as particular fatty acids. And modern anthropoids, considered as a group, meet these needs through a range of diets that include fruit, leaves, insects, flowers, roots, bark, seeds and nuts, and tree gums. As a first approximation, most anthropoids are omnivores. Despite this dietary diversity, they can be classed as faunivores (mainly insectivores), frugivores (fruit eaters), or folivores (leaf eaters) or some combination of these categories.

Dietary choices are in large measure constrained by body size, and anthropoid size has changed dramatically during their evolution. The earliest anthropoid primates, which appeared relatively early in primate history (~55 Ma), weighed less than 100 g. Fossil

evidence on their size and dental structure supports the idea that early anthropoids mainly ate fruits and insects (Fleagle 1999; Rose 2006) and perhaps differed little in this regard from other denizens of the fine-branch niche.

Later anthropoids became larger, and most modern anthropoids weigh more than 1 kg. No major size increases occurred in fossil anthropoids until ~34 Ma, after the platyrhine–catarrhine split (Williams et al. 2010). For example, the fossil anthropoids mentioned earlier in this chapter, *Aegyptopithecus* and *Parapithecus*, were much larger than the earliest anthropoids, weighing 2–4 kg. Once larger anthropoid species appeared, they had adaptations in tooth morphology that indicate a diet comprised mainly of fruits (Williams et al. 2010) and tender leaves (Kirk & Simons 2001; Dominy 2004).

This increase in body size and change in diet occurred along with the expansion of the frontal lobe and the upward grade shift in brain size that we discussed earlier in this chapter. As these animals got larger, they required more energy. So as anthropoids became larger they had to exploit resources in a different way than their ancestors.

As a result, they abandoned the leaping, grasping form of locomotion used by early primates and became arboreal quadrupeds: they moved through the larger tree branches using all four limbs. This conclusion comes from both the prevalence of this form of locomotion in modern anthropoids (Schmidt 2010) and from fossil evidence (Fleagle 1999). Arboreal paths make high demands on energy (Janson 1988), especially when elevation changes during movement. So both their larger size and their mode of movement required a high energy intake.

The new mode of locomotion adopted by advanced anthropoids extended their foraging range. Even taking into account factors such as metabolic rate, modern anthropoids have a surprisingly large home range (Martin 1981). Many anthropoids continued as arboreal quadrupeds, moving through the larger branches with an energy-intensive, acrobatic form of locomotion. A terrestrial mode of quadrupedal locomotion evolved later in several anthropoids (including macaque monkeys), as did the suspensory locomotion of some platyrhine (New World) monkeys and apes, and, of course, bipedalism in the human lineage. Suspensory locomotion allows a re-entry into the fine-branch niche by larger animals. Terrestrial locomotion saves some energy costs compared to arboreal quadrupeds (Janson 1988), but it remains expensive. Bipedalism has many consequences, among them the loss of many hindlimb grasping specializations that evolved in the earliest primates, such as *Carpolestes*.

To sum up our discussion so far, as anthropoids became larger after ~34 Ma, they foraged over a larger range and got much of their nutrition from ripe fruits and tender leaves. These foods have high costs in terms of the energy needed to obtain them and they entail a relatively high risk of predation. Recall that the brain expansion that characterizes advanced anthropoids also occurred after ~34 Ma, the approximate time of the platyrhine–catarrhine divergence.

To understand the nature and intensity of the risks and costs that these animals faced, and how these factors could have led to new granular PF areas, we need to explore the foraging problems faced by anthropoid monkeys.

The anthropoid way of foraging

Most modern anthropoids depend strongly on exploiting resources produced by angiosperm trees, mainly fruits and leaves. Insects are also an important source of proteins and amino acids for many primates, but their biomass and density rarely matches the resources available from angiosperm trees and other plants (Oates 1987).

As advanced anthropoids came to rely on energy-rich products of angiosperm trees, they faced a problem. These resources have a patchy distribution, dispersed throughout their home range. Accordingly, their diet required them to forage more and to rest less. As we have seen, diurnal foragers in the tropics have a limited amount of time to obtain their food because of heat stress and the threat of predation. Given the intensity of the competition and the costliness of their mode of locomotion, these relatively large anthropoids had to make good foraging choices.

Foraging strategies in anthropoids consist in large part of deciding which trees to visit. Any one tree species has its trees dispersed across the home range of a given anthropoid species. Each kind of tree has a characteristic fruiting pattern, usually involving inconsistent fruiting intervals and dramatic variation during the year (Chapman et al. 1999; Janmaat et al. 2006). The same concept applies to leaves. Very few plant species in a given habitat produce nontoxic edible leaves, and trees produce such leaves in a highly seasonal way (Dominy 2004). Only young leaves provide good nutritional value, with high levels of protein relative to fibre. Given that most anthropoids cannot eat or digest much of the plant matter in the tropics, these variations produce frequent and unpredictable food shortages. We propose that this resource volatility provided one of the driving forces for the evolution of new areas in the anthropoid PF cortex.

According to Zuberbühler and Janmaat (2010) large monkeys have a home range that includes ~100,000 trees, of which no more than 4% have ripe fruit at any one time. Janmaat et al. (2006) estimated that for grey-cheeked mangabeys (*Cercocebus*), the home ranges of some groups might have as few as 50 of its 100,000 trees bearing ripe fruit as they move through their territory. Even though their tropical environment has thousands of trees, anthropoid monkeys usually forage on only a small number of tree species at any given time, with a focus on species with a high density of trees and a high density of fruit in each tree (Janson 1988; Eckhardt & Zuberbühler 2004). This foraging strategy makes them vulnerable to any shortfall in fruit production by those tree species, and the same concept applies to the production of nutritious leaves.

Complicating matters further, the proportion of trees bearing ripe fruits or young leaves differs substantially among tree species, and, for a given species, from year-to-year and region-to-region. In one field study, a particular species of tree fruited only four times in 12 years, sometimes producing fruit in 5% of its trees and at other times in 50% of its trees. At one site within a home range, 60% of the trees of a given species had fruit, but at other sites the same kind of tree had no fruit at all (Chapman et al. 2004).

These statistics provide a glimpse of the formidable problems faced by the relatively large animals that anthropoids became. Taken together with the limited time for foraging in the heat, the risk of predation, and the competition from other animals, the inconsistencies in

production by favoured trees must have led to periodic crises in obtaining necessary nutrients. An increased ability to overcome these periods of dearth, while limiting the risk of predation, would have promoted fitness.

We emphasize the idea that this increased ability developed at a particular time and place in the evolutionary history of anthropoids. We do not know exactly when and where these changes occurred, but they probably occurred somewhere in the tropics ~34 Ma. For example, climatic cooling occurred approximately 35 Ma, and it resulted in widespread shortfalls in available resources. As a result, anthropoids needed to diversify their feeding habits to exploit fall-back resources. According to Dominy (2004), leaf eating intensified at this time (Kirk & Simons 2001) and trichromacy may have evolved to distinguish young, nutritious leaves from older ones. As we have seen, the brain expansion of anthropoids began at about the same time and much of this expansion involved the granular PF cortex.

Many sizeable animals need to solve the problem of resource volatility, but we think that anthropoids solved it in a different way, one that depended on their granular PF cortex. Earlier in this chapter, we reviewed evidence that new granular PF areas appeared in anthropoids as their bodies, brains, and frontal lobes became larger. We propose that these new areas allowed them to overcome the problems posed by sporadic food shortages, intense competition, and predation risks. This proposal does not imply that other groups of animals lack the ability to overcome similar problems. After their divergence, each lineage faces up to problems and exploits opportunities on its own, and so parallel evolution occurs commonly.

Field observations have identified some characteristics of foraging strategies that make up the anthropoid way of solving the problem of resource volatility:

1. **Valuation of trees.** Monkeys make foraging choices based on a valuation of individual trees, including species that look identical to all but the most expert anthropoid eyes (Zuberbühler & Janmaat 2010). Anthropoids evaluate individual trees based on prior experience with their fruit and leaves, as supported by evidence that monkeys enter trees more frequently when they had previously eaten high-quality fruit in that tree (Janmaat et al. 2006).
2. **Adaptability during food shortages.** During periods of scarcity, anthropoids that depend on fruits and insects tend to increase their foraging time, rest less, and compete with each other more (Kavanagh 1978; Oates 1987). By contrast, folivores tend to conserve energy and forage less. Frugivorous anthropoids also show marked flexibility at such times, with less preferred foods becoming targets, as fall-back foods. For example, Kavanagh (1978) studied vulture monkeys during a dry-season decline in fruit at two sites. A group of vultures at one site responded by increasing their foraging time and decreasing their dietary diversity, concentrating on eating insects rather than fruit. Another group of vultures responded to the same challenge by decreasing foraging time and increasing dietary diversity, switching from a diet dominated by fruit to a fall-back diet that combined flowers and insects. The differences between these two groups suggest that adaptability—the ability to adopt alternative

foraging strategies—allows anthropoids to overcome irregular shortages in preferred foods.

3. Use of cues and signs. Foraging choices in anthropoids can depend on acoustic and visual cues associated with foods. These signs include sounds made by other primates and avian competitors for the same resource. Janmaat et al. (2006) studied the behaviour of wild mangabeys as they encountered fruits that had just appeared or ripened. When the monkeys neared a tree already occupied by noisy chimpanzees or hornbills, both vigorous frugivores, the monkeys approached more quickly, despite the risk of predation by the chimpanzees.
4. Prediction of food production based on synchrony. Monkeys also use of the discovery of foods in one tree to predict that other trees of the same kind also have available foods. Menzel (1991) studied wild Japanese macaques and found that placing ripe persimmons within their home range induced them to visit persimmon trees, even when the wild trees lacked any ripe fruit. The monkeys must have known the locations of persimmon trees and had learned to predict ripening based on fruits in similar trees.
5. Prediction of food production based on elapsed time. Monkeys appear to monitor and remember a tree's previous food-production history to predict future food availability (Milton 1988). They move significantly faster towards trees with fruit than to trees lacking fruit, even without sensory cues to guide them. And they move even faster to trees with higher quantities of fruit (Zuberbühler & Janmaat 2010).
6. Prediction of food production based on events. Heat, for example, speeds plant metabolism and its production of foods. It also speeds the ripening of fruits. Monkeys make use of recent weather conditions to make foraging choices, returning more quickly to a previously productive tree when it has been hotter (Janmaat et al. 2006).

Summary

Field studies suggest that anthropoid primates face severe resource volatility and the danger of predation, as well as time limitations and competition for resources. Under these conditions, it pays to adapt to periods of food shortages by switching strategies, using distant signs of food availability, and using the memory of a tree's production history to predict where foods will occur, among other approaches.

We suggest that new granular PF areas enabled anthropoids to adapt to the problem of sporadic food shortages in their particular way.

- ◆ Chapter 3 presents evidence that the polar PF cortex allows anthropoids to learn the foraging choice to make in a given context, when that choice has been made just once in the past.
- ◆ Chapter 6 argues that the dorsal PF cortex contributes to making foraging choices on the basis of the order of visual events or elapsed time, as well as to planning sequences of goals in order to improve foraging efficiency.

- Chapter 7 argues that the ventral PF cortex underlies the guidance of foraging choices by visual and acoustic signs, including signs of food availability from near and far as detected by foveal, trichromatic vision.
- Chapter 8 argues that the new granular areas act together to make it possible for anthropoids to adapt to new situations by learning quickly and using abstract rules and strategies, thus using single events to choose foraging goals.

All of these capacities contribute to making better foraging choices, and we propose that new granular areas evolved in the PF cortex to provide anthropoids with these advantages over their ancestors.

Conclusions

The PF cortex evolved in phases, and Figure 2.8 helps to put them in perspective. One phase occurred in early mammals and produced the agranular parts of the PF cortex. Early mammals exploited a nocturnal foraging niche, and the neocortex evolved in these animals. The agranular PF areas, together with new visual, auditory, and somatosensory areas, supported

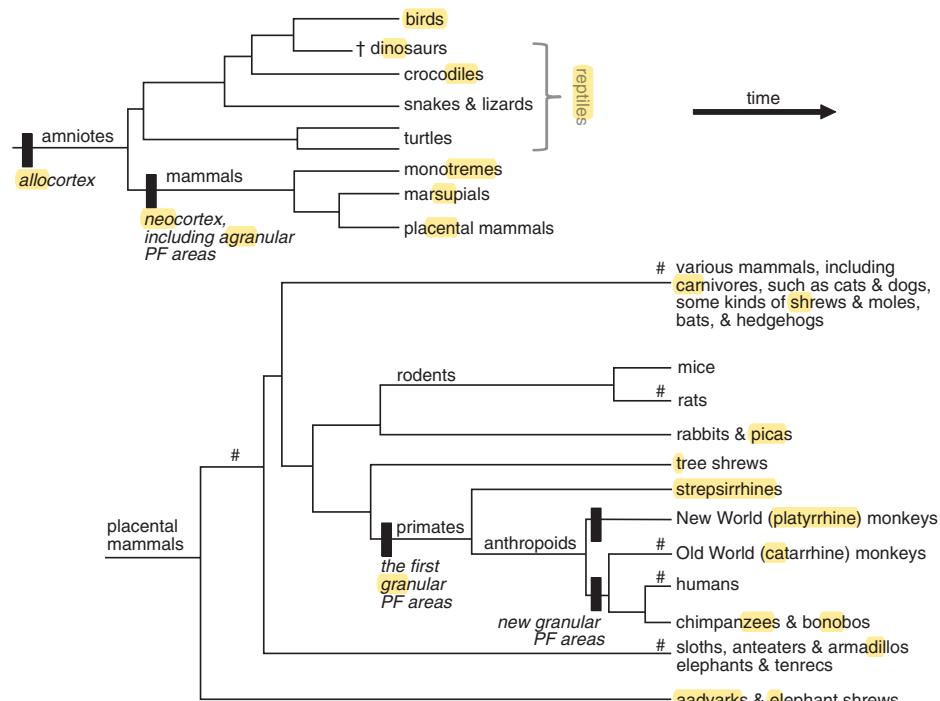


Fig. 2.8 Top: Evolutionary relationships among selected groups of amniotes (birds, mammals, and reptiles). Bottom: Evolutionary relationships among selected placental mammals. Format as in Figure 2.5. The hashtag (#) designates deeply branched lineages that would serve as a sound basis for comparative behavioural studies, as well as their common ancestor. Reproduced from Murray EA, Wise SP, Rhodes SE, What can different brains do with reward? In *The Neurobiology of Sensation and Reward*, ed. JA Gottfried © 2011, Taylor and Francis, with permission.

foraging choices in this new niche. Chapters 3 and 4 discuss the agranular PF areas, and Table 4.1 advances some ideas about their specific contributions to foraging choices.

In a later phase of PF cortex evolution, the granular PF cortex appeared in early primates as they adapted to a life confined to the fine branches of trees, where they could exploit its tender leaves, fruits, flowers, nectar, and insects. The first granular PF areas included homologues of the caudal PF cortex and the granular parts of the orbital PF cortex. These new granular PF areas functioned then, as they do now, in the search for food and signs of food and in the assessment of their value based on current biological needs. Chapters 4 and 5 take up these topics.

A yet later phase of PF evolution occurred during anthropoid evolution. Early anthropoids inherited diurnal foraging and foveas from their haplorhine ancestors, and later anthropoids developed trichromatic vision. As anthropoids became larger, they foraged over a larger home range and came to depend on the food products of particular trees. As a result, they became vulnerable to shortfalls in these foods. The comparative evidence indicates that several new granular PF areas appeared at this time: the dorsal PF cortex, ventral PF cortex, and probably the polar PF cortex, as well. We propose that these new PF areas provided an adaptive advantage during periods of food scarcity and intensified competition. In Chapters 3–8, we argue that these cortical areas improved foraging by reducing the frequency of choices that increased the risk of predation, wasted effort, or yielded fewer benefits than other choices.

In the laboratory, choices that waste effort or yield fewer benefits compared to some alternative are called errors. The clear-cut definition of errors and the other vast differences between laboratory behaviour and natural foraging scarcely need to be mentioned. In the wild, for example, foraging choices frequently involve which tree or location to approach in order to gain food, whereas in the laboratory, responses to stimuli usually involve reaching or eye movements to gain rewards. Foraging often involves the manipulation of objects, including foods, but only a few laboratory tests have explored actions as complex as object manipulation. Laboratory tests have trials, but foraging choices rarely lend themselves to such simple temporal demarcations. And foraging often involves social interactions, which laboratory studies have only begun to examine in any serious way.

Nevertheless, laboratory experiments provide monkeys with choices among places and objects, and these choices produce foods or fluids that they need and consume. Accordingly, laboratory studies can explore cognitive capacities that contribute to successful foraging.

A pioneering study by Hayden et al. (2011b) attempted to model the kinds of foraging choices anthropoids make when they switch from exploiting a dwindling resource to exploring a more distant one. Chapter 3 relates the results of this experiment, but we mention it here because this task serves as an example of using simple coloured shapes, variable delay periods, and saccadic eye movements to study the choices made by anthropoid primates as they respond to visual signs, estimate the travel times to distant resources, and use quadrupedal locomotion to get there.

So despite the obvious differences between foraging in the wild and the constraints of controlled laboratory experiments, many of the cognitive capacities that benefit foraging anthropoids can be studied in the laboratory.

1. Foraging anthropoids need to link their actions with the resource outcomes that follow, and certain laboratory tasks assess how monkeys learn such linkages. Chapter 3 reviews studies in which monkeys learn which action to perform in order to obtain the most resources with the least effort, for example.
2. Foraging anthropoids also need to link foraging goals, such as objects, with resource outcomes. They not only need to learn the general value of a food or fluid, but they also need to evaluate these resources in relation to current needs. Chapter 4 reviews tasks in which monkeys choose among objects associated with some amount or probability of food or fluid. Other experiments can vary motivational factors that reflect current biological needs, for example, by allowing monkeys to consume one kind of food to satiety.
3. In natural foraging, animals see many stimuli at the same time and hold many of them in memory. They need to find their foraging targets amongst all of this clutter and orient their attention to them as they plot the most efficient way to attain their goals. Chapter 5 discusses laboratory tasks that assess attention and search, such as picking out a red square among a field of green ones.
4. Primates benefit when they forage in an orderly and efficient manner, and Chapter 6 discusses many tasks used to study the sequencing of behaviours in time and space, such as learning to navigate a cursor through a visual maze or choosing among 25 opaque doors to obtain the single peanut behind each one. Foraging also involves keeping goals in memory, a concept called prospective coding. Paired-associate learning tasks, in which one stimulus indicates that another one should serve as a goal, can be used to study this function.
5. As they look around, anthropoids see signs of resources. Chapter 7 discusses conditional visuomotor tasks, which examine the mapping of signs to actions. The same task can be used to study how monkeys use abstract strategies. In the wild, this capacity allows anthropoid primates to transfer what they have learned about foraging, in general, to novel or rare foraging problems.
6. In the face of resource volatility it pays to learn from single experiences, and so limit the number of wasteful or risky choices. In the laboratory, this capacity leads to fast learning and other mechanisms for reducing errors. Chapters 3 and 8 review tasks that explore these functions, such as choosing an object embedded in a background scene.

Chapter 1 sets forth the aim of explaining the PF cortex as a whole. But as this chapter shows, the whole has changed over time. The PF cortex that early primates developed lacked many of the granular PF areas that modern anthropoids have; the PF cortex that evolved in early mammals lacked all of the granular areas that primates have. Thus, to fully understand the PF cortex, we need to understand both the parts and the whole. And to do that, we need to take the PF cortex apart. Chapter 3 begins with the medial PF cortex.

事件->目标

输出->目的

输出->动作

->目标

Chapter 3

Medial prefrontal cortex: choosing actions based on outcomes

Overview

The **medial** PF cortex contributes to evaluating and choosing actions based on the previous behavioural outcomes of such actions, and its connectional fingerprint explains how it can do so. Hippocampal connections supply information about navigation and other events that involve actions, the amygdala provides updated valuations of predicted outcomes based on current biological needs, and connections with the medial premotor areas provide a route to action. These ‘internal’ signals, which concern actions and motivations, contrast with external signals such as sensory inputs. Medial PF areas bias the choice of action based on such internal factors, including effort costs, updated valuations, the influence of predicted outcomes on foraging choices, and the use of intrinsic versus extrinsic coordinate frames to guide action. In primates, the granular parts of the medial PF cortex elaborate these ‘internal’ influences by evaluating self-generated choices at feedback time, balancing competing task rules, and making choices based on single prior events.

Introduction

Chapter 1 explains that connections constrain what the PF cortex can do. And because its connections vary region-by-region, this chapter begins a regional exploration of the PF cortex. We start with the medial PF cortex, in part because it includes some of the older parts of the PF cortex (Chapter 2).

Chapter 2 distinguishes *granular* from *agranular* parts of the medial PF cortex, with the latter shared among all mammals. Accordingly, we would like to compare the agranular PF areas in rats and monkeys. Unfortunately, relatively little is known about these areas in monkeys. So we are forced to rely on data from rodents, mainly rats. We recognize the danger of this approach—the last common ancestor of rodents and primates lived ~70–90 Ma and the two lineages have evolved separately ever since. This fact means that changes will have accrued in the connections and functions of the agranular PF areas in both groups of animals as they evolved. Future research will indicate the extent of this divergence, but for now we must make do with what we have.

In primates, the medial PF cortex lies rostral to medial premotor areas, including the preSMA, the SMA, and the CMAs (see the List of Abbreviations). Passingham et al. (2010) have argued that all of these medial areas show a specialization for guiding and analysing actions that are performed on the basis of ‘internal’ signals. The word ‘internal’, in the sense used here, refers to signals that convey internal states and memories, which contrast with external signals such as those for vision, hearing, smell, taste, and touch.

Areas

Figure 3.1 shows the region designated as the medial PF cortex in monkeys and humans, and Figure 2.1 shows one view of its subdivisions in monkeys, humans, and rats. In primates, the agranular part of the medial PF cortex consists of the anterior cingulate cortex (area 24), the prelimbic cortex (mainly area 32), and the infralimbic cortex (area 25). As Chapter 2 explains, all mammals, including rodents and primates, have homologues of these three regions.

The granular part of the medial PF cortex comprises the medial part of area 9 and all of area 10, and only primates have these areas. Chapter 1 justifies the inclusion of the polar PF cortex (area 10) within the medial group of areas, partly based on connections. Note that we include all of the polar PF cortex (area 10) within the medial PF cortex of monkeys, but only its medial part in humans.

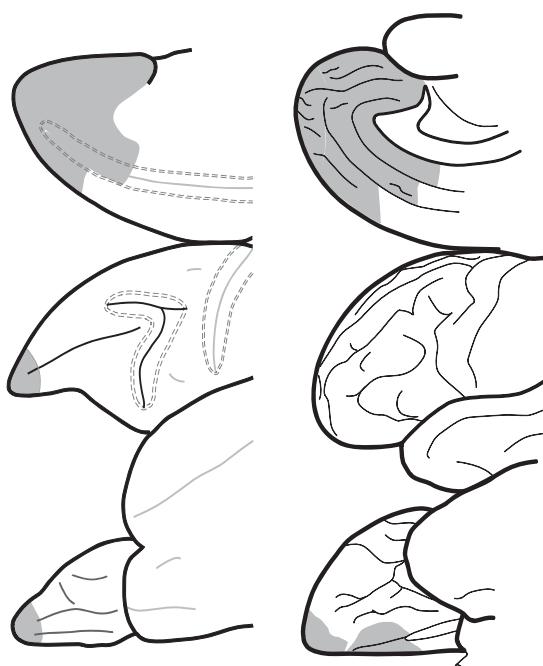


Fig. 3.1 The medial PF cortex in macaque monkeys (left) and humans (right), indicated by shading. Format as in Figure 1.2.

The term anterior cingulate cortex has many meanings in the literature. In this book, we exclude both the prelimbic and infralimbic cortex from the region that we call the anterior cingulate cortex (Figure 2.1). We also exclude the cingulate motor areas, which we consider to be part of the premotor cortex. As a result, readers should be aware that when we use the phrase *anterior cingulate cortex*, we refer only to a part of area 24 and not to either premotor areas or other agranular parts of the medial PF cortex.

Among the areas we exclude from the anterior cingulate cortex, the prelimbic and infralimbic cortex occupy much of the *pregenual* and *subgenual* cortex. The term *subgenual* cortex refers to cortex ventral to the genu of the corpus callosum, and the term *pregenual* cortex refers to agranular areas that lie rostral to the genu. The *pregenual* cortex does not include the granular areas that lie yet more rostrally, such as the medial part of the polar PF cortex (area 10). Finally, the status of area 14, which we call the ventromedial PF cortex, remains uncertain. Some experts include it in the medial PF cortex and others see it as the most medial part of the orbital PF cortex. We do not need to decide between these classifications, but for the most part we reserve consideration of area 14 for Chapter 4 on the orbital PF cortex.

Connections

Figure 3.2 illustrates the main connections of the medial PF cortex in macaque monkeys. This plot and the analogous ones in Chapters 4–7 are intended to convey the most important conceptual points that emerge from the neuroanatomical literature. We do not intend to provide a comprehensive summary, nor are we concerned to indicate which neuroanatomists first described a particular pathway. The plots serve as connectional fingerprints, a concept that Chapter 1 explains. Connectional fingerprints emphasize features that differentiate the regions of the PF cortex from each other and from other cortical areas, much as human fingerprints differentiate people from one another.

1. The hippocampus and subiculum have dense, reciprocal connections with the infralimbic and prelimbic areas of the medial PF cortex (Insausti & Muñoz 2001). Indirect connections between the hippocampus and the medial PF cortex include the anterior cingulate cortex (area 24) and the medial granular areas 9 and 10, and some of these run via the retrosplenial cortex (Kobayashi & Amaral 2003). The entorhinal and parahippocampal cortex also have connections with the medial PF cortex (Kondo et al. 2003; Muñoz & Insausti 2005). Subcortical routes between the hippocampus and the medial PF cortex include a relay via the mammillary bodies and the thalamus.

We take the connections with the hippocampus to be especially important to medial PF cortex function. Other PF areas, such as the lateral OFC, either lack connections with the hippocampus or have very weak ones (Carmichael & Price 1995a). Later, we explain our view that the hippocampus provides the PF cortex with information about navigation and other past events that involve actions.

2. The medial PF cortex has heavy connections with the amygdala, and Figure 3.3 shows that the densest of these projections involve the agranular parts of the PF cortex

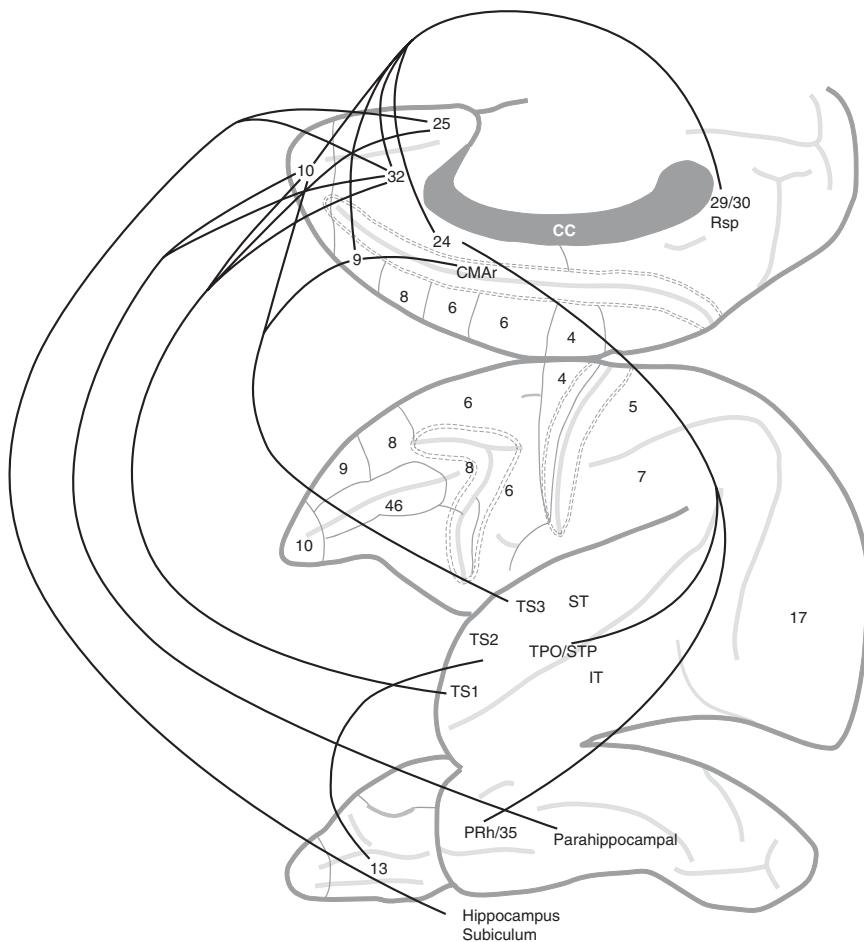


Fig. 3.2 Selected connections of the medial PF cortex in macaque monkeys. Figures 1.4 and 1.5 give the names of sulci and areas. Lines connect some of the areas that have direct axonal connections, assumed to be reciprocal unless otherwise stated.

(Prather et al. 2001; Morecraft et al. 2007). Granular areas, such as area 13m, also receive amygdala inputs that Figure 3.3 does not illustrate (Saleem et al. 2008).

The amygdala is usually viewed as playing a role in emotion, motivation, and reward, including fear conditioning and emotional reactions to social stimuli, such as human faces. But its role in reward is not a general one. Conditional visuomotor learning proceeds perfectly normally after bilateral lesions of the amygdala, even though it depends on learning associations with rewards (Murray & Wise 1996). So reward processing per se cannot be a general or complete description of amygdala function.

Instead, the strongest evidence indicates that interactions between the amygdala and cortex update outcome valuations based on current needs (Baxter & Murray 2002). Throughout this book, we use the word outcome to refer to the feedback that follows

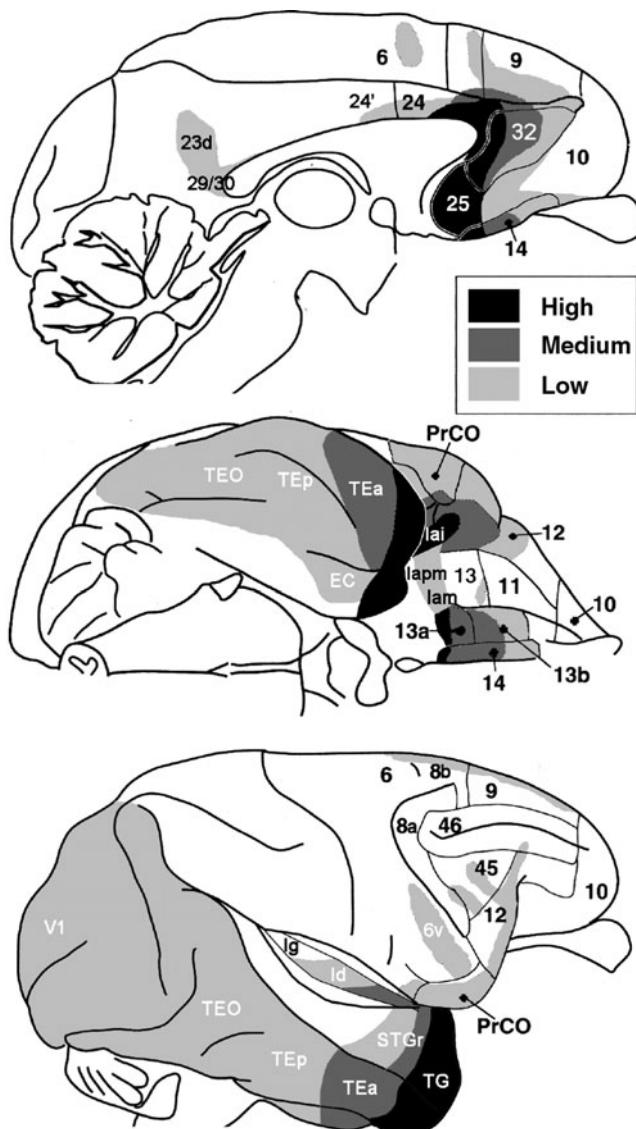


Fig. 3.3 Connections of the amygdala with the cerebral cortex of macaque monkeys. Shading indicates the subjective density of the projections, with emphasis on projections from the amygdala to the cortex. The cortex usually sends a return projection, as well. Abbreviations: EC, entorhinal cortex; lai, lappm and lam, agranular insular areas, inferior, posteromedial, and medial subdivisions, respectively; lg, granular insular cortex; Id, dysgranular insular cortex; PrCO, precentral opercular cortex; STG, superior temporal gyrus; TEa, TEp, TEO, inferior temporal areas, anterior, posterior, and occipital, respectively; TG, temporal pole cortex; V1, primary visual (striate) cortex (area 17). Reprinted by permission from Macmillan Publishers Ltd. Price JL, Drevets WC. Neurocircuitry of mood disorders, *Neuropsychopharmacology* 35:192–216, © 2009, Nature Publishing Group.

an action, both in terms of what occurs and what that is worth at any given time. Of course, current needs not only involve nutrients and fluids, but also harm avoidance and other biological costs and benefits. Accordingly, we can say that the amygdala contributes to evaluating both positive and negative outcomes.

3. The medial PF cortex projects, both directly and indirectly, to premotor areas. The granular medial PF cortex (area 9) has connections with other parts of the medial PF cortex, specifically with the anterior cingulate cortex (Vogt & Pandya 1987). This area, in turn, connects with the rostral cingulate motor area (CMAr), a part of the medial premotor cortex (Morecraft & Van Hoesen 1998). The CMAr lies in the cingulate sulcus (Dum & Strick 2002), ventral to the presupplementary motor area (preSMA), with which it is connected (Luppino et al. 1993). The SMA proper is also interconnected with the caudal cingulate motor area (Luppino et al. 1993).

Lesions of either the cingulate motor areas or of the preSMA and SMA impair the generation of movements that monkeys make without being prompted by external (sensory) cues (Thaler et al. 1995). Accordingly, we can refer to these actions as being ‘internally’ guided.

4. Unlike the ventral PF cortex and the orbital PF cortex, the medial PF cortex does not receive visual inputs from the inferior temporal cortex (Carmichael & Price 1995b; Kondo et al. 2005). However, the anterior cingulate cortex has some connections with the perirhinal cortex, and it also receives inputs from area TPO in the superior temporal sulcus (Kondo et al. 2005), which processes both visual and auditory information. Notwithstanding these inputs, connections between the medial PF cortex and visual areas are not particularly prominent.
5. The medial PF cortex, and especially the polar PF cortex (area 10), receives projections from the superior temporal cortex, most of which come from its rostral part, including the temporal pole (Barbas et al. 1999; Kondo et al. 2003).

Some of the more caudal of these projections involve areas that have been shown by physiological studies to be auditory (Hackett et al. 1998), but the functions of the others, such as those nearer the temporal pole, remain unknown.

6. Unlike many other parts of the PF cortex, the medial PF cortex also projects to the hypothalamus (Rempel-Clower & Barbas 1998), as well as to brainstem reticular nuclei that play a role in visceromotor function (Öngür et al. 1998; Barbas et al. 2003).

Some of these projections probably influence the autonomic nervous system, along with other ways that the brain controls the body. The lateral hypothalamus regulates autonomic arousal, for example, and the paraventricular nucleus of the hypothalamus controls neuroendocrine and neurosecretory outputs.

Summary

The connectional fingerprint of the medial PF cortex suggests the following main points: (1) the medial PF cortex receives a paucity of sensory inputs compared to other parts of the PF cortex; (2) it is connected with premotor areas that control actions when animals

lack a prompt for the action from any external cue; and (3) it has strong connections with the hippocampus and the amygdala, which suggests that it has access both to memories of past events and also to information about outcomes as valued in terms of current biological needs.

Although the connections listed here do not always involve the same parts of the medial PF cortex, the various parts connect with each other (Barbas 2000), and this means that the inputs to one can influence the others. Chapter 8 expands this idea to the PF cortex, as a whole.

Decisions, choices, and goals

Although the term *decision* can be applied to most things that animals do, we use the term in a more restricted way. We distinguish decisions from the *choices* and *actions* that might follow such decisions (Schall 2001). Decisions involve perceptions based on sensory inputs. In this sense, a decision does not refer directly to anything that an animal does. Thus animals make perceptual *decisions*, not perceptual *choices*. And they make foraging choices, not foraging decisions.

As a result of its decisions, an animal might choose a *goal*, and based on the choice of this goal, it might choose an action. Alternatively, an animal might choose among actions directly. Throughout the book, we use the term goal to refer to the objects or locations that an animal chooses as a target for its actions. The action then produces an outcome, which involves the benefits that the animal receives or the costs incurred as a result of its behaviour. We thus distinguish goals from outcomes and never use the term goal as a synonym for outcome.

We know that it is common in the literature to use the term goal for the reward that an animal receives in behavioural experiments. And, indeed, in these experiments the reward serves as the animal's ultimate goal. But in order to obtain a reward the animal usually has to choose an object or location as the target for its action. So we reserve *goal* for those objects and locations and consistently use *outcome* for rewards and other forms of feedback about actions or events. This terminology facilitates the discussion at many places in this book, and readers need to bear in mind the way that we use these terms and how that differs from other uses in the literature.

We also distinguish between choices based on external or 'internal' cues (Passingham et al. 2010). For example, monkeys can use distant visual signs to choose a foraging goal such as fruit or leaves in a distant tree. They thus generate a goal—the fruit or leaves—based on an external, sensory signal. But monkeys can also generate a goal on the basis of their memory or a change in their internal state, such as hunger. For want of a better word, we say that in this case the animals act on the basis of 'internal' signals. Later, we discuss the role of medial PF cortex when external and 'internal' signals compete.

Accumulator networks

Accumulator–racetrack models provide a mechanism for this kind of neural competition, and so we give a very brief account here. Although accumulator networks have been

best characterized for visual motion and oculomotor areas, understanding these models will make it easier for readers to understand how inputs to the medial PF cortex could lead to actions and how outputs from the medial PF cortex might bias other, similar networks elsewhere. Later in this chapter, we will see a specific application of these ideas to the function of the medial PF cortex in making choices like those made in foraging.

Neurophysiological experiments in monkeys illustrate how accumulator networks work. Decisions, choices, and actions occur when neural networks reach a threshold for producing an output. These networks act like leaky integrators, accumulating ‘evidence’ in favour of their output: the decision, choice, or action that the network represents. Once they reach their threshold, the output of the network causes a series of effects that can end in the execution of a motor command, either by driving activity in motor pattern generators or releasing them from tonic inhibition. Accumulator networks of various types operate in parallel and so can be said to compete with each other.

Figure 3.4 shows results from a pop-out experiment. In experiments of this kind, a number of stimuli appear in the visual field of a monkey. Most of them have the same features, such as colour and shape, but one differs. In the experiment that led to Figure 3.4, the monkey saw seven red squares and one green square, and these eight

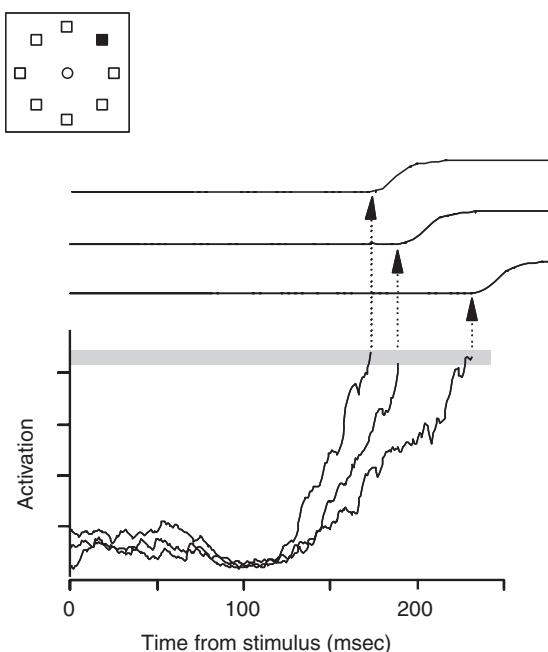


Fig. 3.4 Neuronal activity in the frontal eye field. Discharge rate as a function of time after stimulus onset. As activity increases, it reaches the threshold (shaded horizontal bar) for a saccadic eye movement. The trials are divided into thirds based on response latency. The inset in the upper left shows the display observed by the monkey, in which one stimulus ‘pops out’ from a set of eight stimuli because of its different colour (black square). Reproduced from Schall JD, Thompson KG. Neural selection and control of visually guided eye movements. *Annual Review of Neuroscience* 22:241–59 © 1999 Annual Reviews, with permission.

stimuli appeared equally spaced at the circumference of a circle centred on the fixation point. To receive a reward on each trial, the monkey had to make a saccadic eye movement to fixate the green square. As in all tasks, the amount of time from the appearance of the eight stimuli until the onset of the monkey's movement, called the reaction time, varied from trial to trial, but usually fell in a range from 175–225 ms. The fact that this experiment involves eye movements becomes important in Chapter 5, but for the present purpose the kind of movement does not matter.

Accumulator models assume that some accumulators integrate evidence for a green stimulus. One could say that these accumulators embody a 'hypothesis' that the stimulus is green and its inputs serve as evidence for and against this hypothesis. At the single-cell level, the accumulation of information appears as activity that ramps up until it reaches the threshold, sometimes called climbing activity. Figure 3.4 shows this climbing activity divided into three groups of trials, sorted according to the monkey's reaction time. For the shortest reaction times, the cell ramped up to a given level, designated by the horizontal grey bar, and the saccade began shortly thereafter. No direct evidence says that an entire network of such neurons reached a threshold at that moment, but we assume so. As the figure also shows, a slower rate of activity increase corresponded with the longer reaction times.

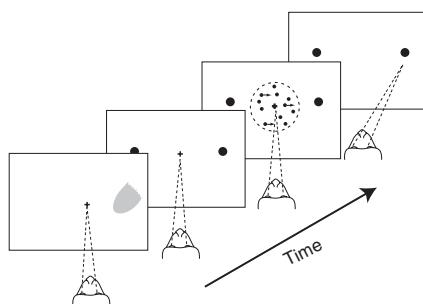
The competition arises because of the architecture of these neural networks and their interaction. The network that first reaches threshold 'wins' the race, and it controls the decision, choices, or actions that it represents. Collectively, these circuits work in a winner-take-all manner, which reflects the fact that an animal cannot move two opposing directions at the same time, and, likewise, in most circumstances does not make contradictory decisions and choices simultaneously.

Experiments in which a monkey has to discriminate the direction of coherent motion illustrate the way in which accumulator networks compete. In this task, many spots of light move in the same direction at the same speed while other spots move randomly. The accuracy of decisions improves with longer viewing times and when more spots move in the same direction. Gold and Shadlen (2007) have reviewed the evidence for these neuronal mechanisms. According to their analysis, cells in several areas increase their activity until they reach a threshold: networks in areas MT and MST represent decisions, those in area LIP represent choices, and those in the FEF represent actions (Kim & Shadlen 1999).

Figure 3.5 shows how top-down biased competition can work. In this case, the experimenters used intracortical microstimulation in area MT to simulate a top-down signal. Take a network that integrates evidence for upward movement, for example. By exciting neurons in that network, it reaches threshold faster than without the microstimulation. This artificial input makes it more likely that the 'upward' accumulators will win the 'race' and produce the decision that the dots are moving upward.

The rate at which activity ramps up to the threshold of a network, and thus generates a decision, choice, or action depends on both the strength of the evidence and the time available to integrate the evidence. And it also depends on the activity of competing accumulators, those that gather evidence for alternative decisions, choices, and actions.

A



B

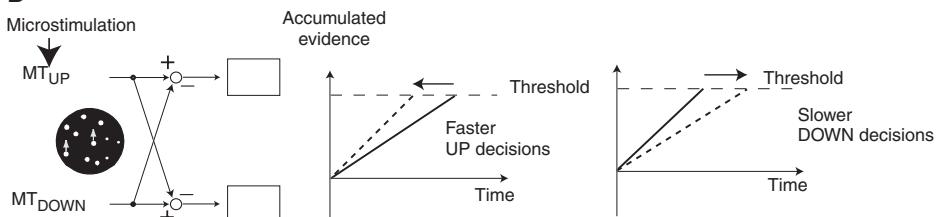


Fig. 3.5 Neural mechanism of top–down attention. (A) Monkeys view spots and choose between a left and right saccade target to report the direction of spot movement. The dashed lines converge at the fixation point. (B) Some accumulator networks integrate evidence for dots moving up, others for dots moving down. When the dots are moving up, greater activity in the network, due to intracortical microstimulation, leads to its reaching the threshold for an ‘up’ decision faster and a ‘down’ decision slower (dashed lines). Abbreviations: MT_{UP}, cells in the middle temporal area encoding upward spot movement; MT_{DOWN}, cells encoding downward movement. +, excitatory synaptic inputs; -, inhibitory inputs. Dashed lines show the activity rate during intracortical microstimulation; solid lines show activity before and after such stimulation. (A) Reproduced from Roitman JD, Shadlen MN. Response of neurons in the lateral intraparietal area during a combined visual discrimination reaction time task. *Journal of Neuroscience* 22:9475–89 © Society for Neuroscience, 2002 with permission. (B) Reproduced from Ditterich J, Mazurek ME, Shadlen MN. Microstimulation of visual cortex affects the speed of perceptual decisions. *Nature Neuroscience* 6:891–8 © 2003.

As an important aspect of the ‘race’, cells accumulating contradictory evidence can inhibit each other, as illustrated in Figure 3.5. Other factors also affect each ‘race’, including the threshold of each network, its level of excitability, and signals that countermand or veto the decision, choice, or action. Taken together, the interactions among many of these networks allow hierarchically higher networks to bias the results produced by lower-order ones. For the medial PF cortex, this involves interactions with the hippocampus, amygdala, premotor cortex, hypothalamus, periaqueductal grey, and other structures.

In later chapters, we argue that other areas of the PF cortex also act to bias competition that takes place in lower-order areas. For example, Chapter 5 presents evidence that the caudal PF cortex can exert a top–down bias on visual areas in order to enhance the processing of motion or shape, depending on their relevance to the task at hand. Likewise,

Chapter 8 argues that the PF cortex, as a whole, exerts a top–down influence when the task requires the attentive control of behaviour.

Summary

Like single cells, accumulator networks integrate inputs and, when they reach a threshold, they produce an output. These models provide a plausible neuronal mechanism for decisions, choices, and actions in terms of evidence and representations, rather than merely inputs and firing, as embodied by the concept of the ‘grandmother cell’.

To summarize the chapter to this point, the medial PF cortex has a unique set of connections, which is characterized by a paucity of sensory inputs and close interactions with the hippocampus, amygdala, and medial premotor cortex. Some of these connections drive networks in the medial PF cortex, and some convey outputs from the medial PF cortex to other parts of the brain, where they provide a top–down bias. In the next section, we present some of the evidence that the agranular parts of the medial PF cortex bias the competition among lower-order systems that compete to control behaviour.

Agranular cortex in rodents

Murray et al. (2011) proposed that by biasing the competition among brain systems that vie to control behaviour, the medial PF cortex can affect an animal’s action without directly generating motor commands. This idea explains how the ancestors of mammals could get along so well without a medial PF cortex. In the absence of these areas, the strongest associations among the competing systems prevail. This balance of power can change, but only slowly. When it evolved in early mammals, the agranular PF cortex provided a top–down bias that promoted faster changes, not an entirely new capacity for change. Later, especially in Chapters 8 and 9, we propose that this kind of advance—faster changes, fewer errors—occurred repeatedly during the evolution of the PF cortex, and Chapter 5 takes up a more general treatment of top–down biased competition.

A great deal of vertebrate behaviour depends on the phylogenetically old mechanisms of reinforcement learning. These include classical (Pavlovian) and instrumental (operant) conditioning (Dickinson 1980). In traditional animal learning theory, reward strengthens the associations that are active in its presence, a process called reinforcement. Through this reinforcement-learning mechanism, associations develop between representations of stimuli, responses, and outcomes. Each representation can link to other representations, and they can be abbreviated as S, R, and O, respectively. In classical conditioning, the stimulus S becomes associated with an outcome O, which one can call an S–O mapping. In instrumental conditioning, the response R becomes associated with an outcome O, called an R–O mapping. In the latter case, this association may occur in a particular stimulus context S, giving rise to S–R–O mappings. The terms response and action differ little in meaning. The former often implies the existence of a stimulus to start things off, whereas the latter need not. We use the compact notation of S–R, R–O, and so forth from time to time as convenient, without distinguishing between actions and responses.

After animals gain extensive experience with particular S–R–O and R–O associations, their behaviour loses its dependence on the outcome and becomes a habit. The term procedural memory is sometimes used to refer to habits, being contrasted with declarative memories. We avoid the use of these terms because the concept of declarative memory typically implies consciousness, and we can say nothing about a human-like consciousness in nonhuman animals.

Balleine et al. (2003) used a simple procedure for distinguishing outcome-directed actions from habitual actions. Experimenters can operantly condition an animal to perform a given action, which produces one kind of reward outcome. They also can condition the same animal to perform a second action, which produces a second kind of reward outcome. In general, the subject finds both kinds of rewards desirable, although they often have a preference. Next, the subject gets the opportunity to consume one of the two rewards, typically to satiety. Consuming this reward devalues it relative to the alternative. In later testing, called the test phase, the subject can choose between the two actions. Unless they have developed some kind of habit, the subjects will spend most of their time working for the most valuable reward, as assessed in terms of their current needs. This means that they avoid the action that produces the recently consumed reward. Satiation on one of the rewards thus affects their choice of action.

Most psychologists call behaviours with this property goal-directed. But as we have already mentioned, we reserve the word goal to refer to the target of action. So we call these behaviours outcome-directed instead.

It is an important feature of these experiments that the animals choose their action prior to receiving any reward outcome in the test phase. That is, they do not need to experience the devalued food in their current, sated state. Instead, the subjects predict the value of the reward that their actions will produce and make their choice accordingly.

After the animal has gained so much experience on this kind of task that they have developed a habit, satiation on one of the rewards ceases to affect its actions. The animal continues to choose the action that has led to a given outcome in the recent past, usually a preferred food, even though that outcome has been devalued. Habits are also called S–R associations because the animals choose an action without reference to the predicted outcome. The amount of training needed to produce a habit is called *overtraining*.

Note that some experts use the term habit in a less rigorous way to refer to just about anything that an animal does frequently or that people can do without thinking about it. So readers need to know that we do not use habit in this expansive way.

Earlier, we explained the basic principles of accumulator–racetrack models. Now we can apply these principles to the generation of habits in overtrained animals. According to accumulator–racetrack models, habits prevail once S–R associations become sufficiently strong that their accumulator networks always reach their threshold before any competing networks can reach theirs. For example, assume that S–R networks compete with S–R–O networks. We suppose that as connections strengthen in the S–R networks, they will reach their threshold faster. When this process reaches the point that no other network can possibly ‘win’ the race, a habit has been formed. When one kind of

association dominates the others, it can be called *prepotent*, and the phrases *prepotent behaviour*, *prepotent response*, and *prepotent action* all refer to this idea. These terms apply both to innate behaviours and to those inculcated by extensive experience. Prepotent behaviours provide an advantage in relatively stable environments.

However, a reliance on prepotent behaviours has costs as well as benefits. They have the disadvantage that the animal can only adapt to new conditions relatively slowly. In one classic example, green lizards (*Lacerta*) have an innate tendency to approach the colour green because it guides them towards leaves that provide camouflage and the opportunity for capturing prey. Wagner (1932) tried to teach these lizards to choose between a red stimulus that was associated with a desirable food and a green stimulus that was associated with the same food in an adulterated form. It took hundreds of trials to train the lizards to choose the red stimulus, and some could not do so, even though they could easily discriminate red from green. The lizard's prepotent behaviour works well in their usual niche, but as a result they cannot adapt flexibly to a volatile environment.

Yet mammals can learn this task relatively quickly. Murray et al. (2011) provide additional examples of behavioural inflexibility in nonmammalian vertebrates, in contrast with mammalian flexibility. Rats, for example, can learn the matching-to-position task. In this task, rats must learn to return to a place in which they have just received food (Marighetto et al. 1998). To perform this task successfully, rats must overcome an innate tendency to explore foraging sites that they have not exploited recently and avoid those that they have. Intact rats can learn this task in 15–20 training sessions, but after lesion of the prelimbic and infralimbic areas of the medial PF cortex, rats learn much more slowly (Dias & Aggleton 2000). The medial PF cortex thus seems to confer the ability to switch from prepotent behaviours more rapidly and with fewer errors compared to animals lacking these areas.

Another observation strengthens the idea that the lesioned rats cannot easily overcome their innate tendency: the same lesioned rats can learn the nonmatching-to-position task at approximately a normal rate (Dias & Aggleton 2000). On this task, the animal must avoid the location where they have just received food and choose the alternative arm of the maze. The rats therefore do not have to overcome their prepotent tendency to avoid recently exploited foraging sites. These ideas explain why rats with prelimbic and infralimbic cortex lesions can learn the nonmatching-to-position task at a normal rate but learn the highly similar matching-to-position task at an abnormally slow rate.

In the wild, the tendency to vary foraging sites provides advantages in many circumstances. Depleted food sources provide little benefit. However, in some circumstances, such as when a resource replenishes unusually rapidly, the advantage goes to an animal that can learn the context in which this renewal might occur and can suppress the prepotent tendency to look elsewhere for food. In this way, the top-down biasing of subcortical brain systems can provide an enhanced level of flexibility in foraging choices, and the medial PF cortex seems to provide this capacity in mammals. Table 3.1 lists some of the problems that animals face in choosing actions and some of the advantages that the medial PF cortex might bring.

Table 3.1 Fundamental problems in choosing actions

Problem	Solution
Different actions produce diverse outcomes in terms of payoff and effort	Bias foraging choices based on learned action–outcome associations
Actions can be based on either extrinsic or intrinsic coordinates	Bias foraging choices toward those based on extrinsic or intrinsic rules ^a
Actions can occur in either stable or volatile environments	Bias foraging choices toward those based on habits or those based on predicted outcomes, respectively

^a Often called ‘place’ rules and ‘response’ rules, respectively.

Prelimbic cortex and outcome-directed behaviour

In rats, the medial PF cortex comprises three areas, the anterior cingulate cortex, the pre-limbic cortex, and the infralimbic cortex (see Figure 2.1). As we have already mentioned, the results from the matching- and nonmatching-to-position tasks help elucidate the role of the pre-limbic and infralimbic cortex, but do not distinguish between them. However, several studies have attempted to do so.

Lesions of the pre-limbic cortex impair the ability of a rat to modify its behaviour when the value of the outcome changes. The devaluation test described in the previous section reveals the ability of animals to adjust choices according to current needs. Rats with pre-limbic cortex lesions continue to make responses that yield highly devalued rewards. Thus lesions of the pre-limbic cortex lead to the dominance of habitual over outcome-directed behaviour (Balleine & Dickinson 1998; Corbit & Balleine 2003). So, we can conclude that in normal rats the pre-limbic cortex generates a bias toward foraging choices based on outcome-directed behaviour, as opposed to habits.

Pre-limbic cortex lesions that occur after learning do not have this effect (Ostlund & Balleine 2005), which also agrees with the idea that this area generates a bias toward outcome-directed behaviour. S–R associations (habits) develop at the same time as S–R–O associations. After extensive experience, habits can control behaviour, and so the influence of the pre-limbic cortex becomes less important.

The infralimbic cortex seems to provide the opposite bias. Killcross and Coutureau (2003) found a double dissociation between the roles of the pre-limbic and infralimbic cortex. They confirmed the finding, just mentioned, that lesions of pre-limbic cortex render rats insensitive to current reward value as manipulated experimentally. Lesions of infralimbic cortex did not have this effect. After these lesions, the rats’ choices remain affected by the current value of the reward, even after the kind of lengthy overtraining period that would normally yield habitual behaviour. We can conclude, therefore, that in normal rats the infralimbic cortex provides a bias toward habits. Without that bias, behaviour remains outcome-directed even in situations in which habits would be expected.

These findings indicate the role that these areas play in normal rats: the pre-limbic cortex biases behaviour toward foraging choices based on S–R–O associations (outcome-directed behaviour), whereas the infralimbic cortex generates biases toward the simultaneously

learned S–R associations (habits). Put more broadly, these areas seem to influence the competition between S–R–O and S–R associations for control of choices among actions.

If so, why does the medial PF cortex need two areas to generate this influence? One area should suffice because more habitual action means less outcome-directed action and vice versa. The existence of two competing areas makes sense if they each learn a context for emphasizing the kind of behaviour that they favour. An experimental finding supports this idea. After overtraining, temporary inactivation of the infralimbic cortex reinstated outcome-dependent behaviour even after a habit had developed (Coutureau & Killcross 2003). Although other interpretations of this result are possible, it is as if the rat failed to recognize the context for performing its habit.

From an ecological perspective, the competition between the two areas provides the ability to learn the contexts for foraging in conditions of differing resource volatility and to switch rapidly between them. In low-volatility conditions, habits should prevail because it pays to respond quickly in routine situations. When volatility increases enough that the routine behaviour fails more than occasionally, but not so much that outcomes become completely unpredictable, it pays to switch to making foraging choices based on predicted outcomes.

Prelimbic cortex and competition among rules

The distinction between outcome-directed and habitual performance also helps to explain the results of experiments on rule switching. In these studies, rats with inactivation of the prelimbic and infralimbic cortex switch between foraging choices based on two different rules.

A classic paradigm involves the training of rats on a maze with four arms, known as a plus maze (Figure 3.6). On each trial, the rat begins at the end of one arm, and when it reaches the junction of all four arms it has to choose between the left and right arms. The rat can use two rules to make this choice. The first rule uses intrinsic coordinates: turn in a particular direction, for example, to the right (Figure 3.6, top right). The second rule uses extrinsic coordinates: turn to the east, for example (Figure 3.6, top left). This second rule depends on cues external to the maze, often called extramaze cues. Experimenters have applied many names to these two tasks, and Chapter 1 warns about task names. The term *response rule* has been applied to the intrinsic-guidance task, and *place rule* has been used to describe the extrinsic-guidance task. Because the place rule also requires a response, we prefer other names. So for the present purposes, we use the terms intrinsic and extrinsic rules, instead of response and place rules.

Some neuroscientists have equated the use of intrinsic coordinates with habits, but this is a misconception (Table 3.1). We pointed out earlier that animals can choose objects or places as their goals or they can choose actions directly. When using extrinsic coordinates, an animal chooses a place as its goal; when using intrinsic coordinates, it chooses an action directly. Both can be habitual or outcome-directed. Of course, once an animal becomes very familiar with a behavioural situation—a certain maze, for example—*intrinsic coordinates will tend to predominate*, but this does not mean that the use of *intrinsic coordinates equates with habits*.

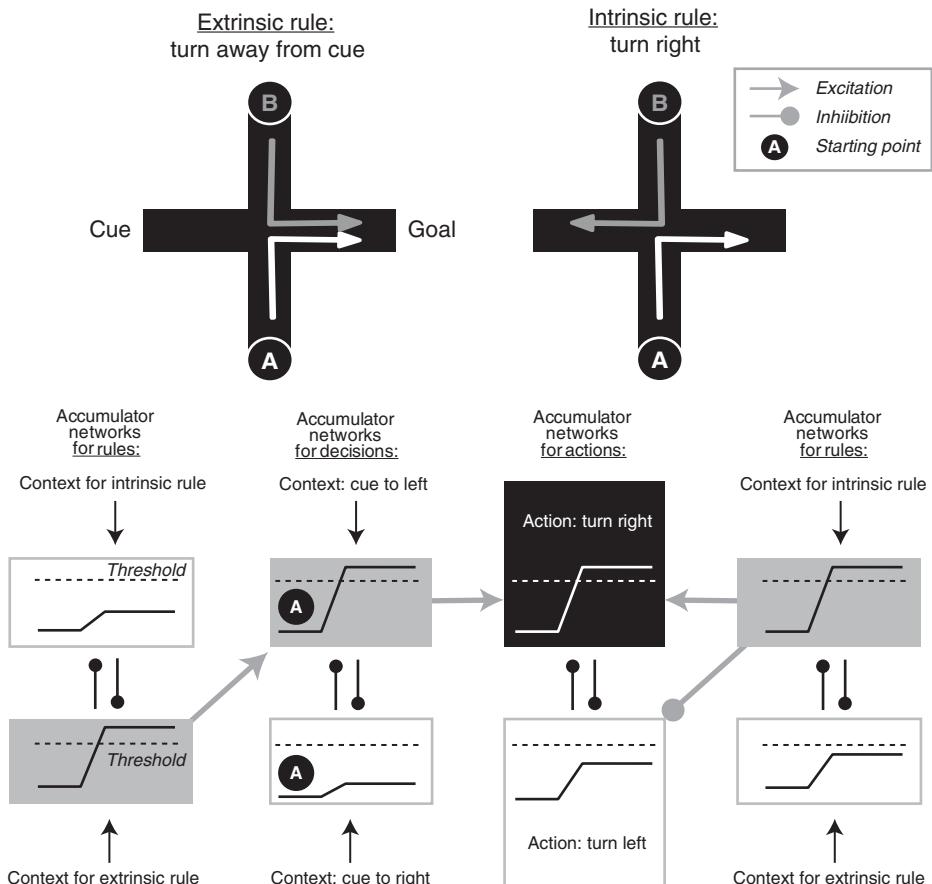


Fig. 3.6 Accumulator network model of choices based on extrinsic versus intrinsic rules. Top: rats begin each trial at either point A or B of a plus maze. For the extrinsic rule, they need to choose a goal opposite a visual cue, east in this example. For the intrinsic rule, the rats need to turn right at the choice point. Bottom: conceptual depiction of how accumulator networks lead to a right turn (black background) for both rules (grey background). For example, when accumulator networks encoding the extrinsic rule (bottom left) reach threshold, their outputs inhibit networks encoding the intrinsic rule (top left) and facilitate networks encoding the sensory evidence that the cue is to the left, given that the rat begins the trial at point A. These networks, in turn, provide evidence to networks encoding the right turn in this condition. By contrast, for the intrinsic rule, different networks (upper right) reach threshold first and facilitate right turns while inhibiting left turns. Key: circled letters show possible starting points.

An experiment by Ragazzino et al. (1999) used the plus maze with odour cues. Having trained the rats to use one rule, Ragazzino et al. then trained them to use the other one. This new learning involved suppressing or surmounting the rule that had become habitual. Inactivation of the prefrontal and infralimbic cortex did not impair the ability of rats to learn the initial rule, whichever one they had learned first. But the lesion did impair the ability to switch to the second rule. To confirm that the key factor involved

switching between two rules, as opposed to switching responses in general, Ragazzino (2007) tested the rats on switching between the choice of two odours, and the rats performed normally.

Rich and Shapiro (2007) extended these results using visual extramaze cues. Inactivation of the prelimbic and infralimbic cortex led to an impairment in switching between the intrinsic and extrinsic rules but did not affect the ability of rats to perform reversals of their choice within either rule. Importantly, inactivation did not disrupt performance on the day of the rule switch. Instead, the lesion caused an increased and incorrect use of the older rule on tests performed the next day.

Rich and Shapiro (2009) also recorded neuronal activity in the prelimbic and infralimbic cortex during the rule switch. They found that activity changes occurred earlier in the prelimbic cortex than in the infralimbic cortex. The change in activity in infralimbic cortex occurred when foraging choices had improved after a rule shift. This finding probably reflects the bias toward outcome-directed behaviour that the prelimbic cortex provides, in contrast to the bias toward habitual behaviour that the infralimbic cortex affords. In general, cells in these areas encoded switching between the intrinsic and extrinsic rules but not switching within rules.

These results implicate the prelimbic and infralimbic cortex in guiding changes in foraging rules based on competing coordinate frames. As rats attempt to learn a second rule, they have to use outcome-directed behaviour to do so and they need their prelimbic cortex to produce the appropriate bias. Without this bias, habits from the first rule interfere with learning the second. If this second foraging rule remained productive for a long time, the rat would eventually use this rule as a new habit. Figure 3.6 shows how accumulator networks could implement these rules, and Chapters 6–8 take up the role of the PF cortex in learning and applying rules in more detail.

The discussion to this point has focused on the prelimbic and infralimbic parts of the medial PF cortex. The next section examines the role of its remaining agranular component, the anterior cingulate cortex.

Competition between benefits and costs

When faced with a choice between two actions, animals must take into account not only their relative benefits but also their relative costs. In the laboratory, experimenters can give an animal a choice between a large reward that comes at a large cost and a small reward that comes at a small cost. As an example of costs, experimenters can require rats to climb over an obstacle in order to gain the reward (Salamone et al. 1997) or to wait before gaining it (Cardinal et al. 2001). The first manipulation imposes an energy cost; the second imposes a delay cost.

Walton et al. (2003) tested rats with medial PF lesions using the first of these manipulations. The rats had to choose between two arms in a T-maze. At the end of one arm, the rats could obtain a large reward but they could reach it only by climbing over a difficult barrier; at the end of the other arm they could obtain a small reward without the effort needed to surmount the barrier. Normal rats chose the larger of two rewards even though they had to climb a considerable barrier to get to it. However, rats with lesions of the

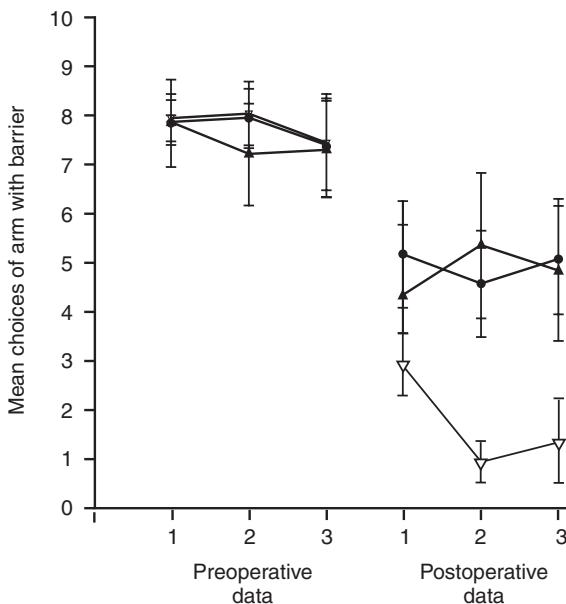


Fig. 3.7 Effect of effort costs on goal choices in rats. Three groups of rats choose between two arms of a maze. One arm had a small reward and no barrier; the other had a large reward and a 30-cm high barrier that the rats needed to surmount. The ordinate shows that mean number of times that the rats chose the high-effort arm, out of 10 trials. Postoperatively, rats with lesions of the anterior cingulate cortex (unfilled triangles) chose the high-effort bar significantly less frequently than the other two groups: rats with sham lesions (filled circles) and rats with prelimbic plus infralimbic cortex lesions (filled triangles). Error bars: SEM. 1, 2, and 3 on the abscissa show the data for 3 days of testing with ten trials each. Reproduced from Walton ME, Bannerman DM, Alterescu K, Rushworth MF. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions, *Journal of Neuroscience* 23:6475–9 © Society for Neuroscience, 2003, with permission.

anterior cingulate cortex chose the smaller reward under these conditions (Figure 3.7). It takes a considerable increase in the amount of the larger reward to induce the rats to climb the barrier (Walton et al. 2002).

Rudebeck et al. (2006b) compared the effects of manipulating costs in terms of either effort or delay. Lesions of the anterior cingulate cortex in rats disrupted choices based on effort, whereas lesions of the orbital PF cortex caused an impairment in choices based on delays in obtaining reward. Because the study involved rats, we know that the lesions involved the agranular areas. We take up the results from these parts of the orbital PF cortex in the next chapter, but for now we can conclude that both the medial parts of the agranular PF cortex and the orbital parts take into account evidence about costs and benefits, with some specialization for the kinds of costs involved. We do not know that the same conclusions apply to monkeys, but we assume that they do.

When a behaviour does not involve a foraging choice, anterior cingulate lesions do not impair behaviours that depend on effort costs. Schweimer and Hauber (2005) required

rats to press a bar more and more often to obtain food, and anterior cingulate lesions did not affect this behaviour. If the lesions simply rendered the rats lazy or apathetic, they would have stopped pressing the bar when they needed to make many bar presses in order to produce food. The experiments of Walton et al. (2002) and Schweimer and Hauber (2005) differ in that in the former case the rats had to *choose* between two actions but in the latter case they did not. The results of the experiment by Walton et al. imply that the lesioned rats overrate the effort costs or underrate the reward benefits when they have to make a foraging *choice* based on predicted outcomes.

Summary

To sum up this section, we have used evidence from rodents to argue that the agranular parts of the medial PF cortex function as follows:

1. They bias the competition among phylogenetically older behavioural-control systems to speed adaptability in foraging choices.
2. They bias foraging choices toward either habits, which are appropriate for a stable resource environment, or toward outcome-directed behaviours, which are appropriate for conditions of moderate resource volatility.
3. They bias navigational choices between extrinsic and intrinsic rules to guide foraging choices.
4. They play a crucial role in a cost–benefit analysis when animals must choose between actions based upon the value of predicted outcomes, including effort costs.

In this selective review, we have emphasized the current biological value of an outcome in terms of rewards. The valuation of outcomes, of course, extends more broadly to encompass other kinds of costs, such as the threat of predation or other forms of harm, and other kinds of benefits, such as social ones.

The connections of the medial PF cortex determine how it can perform these functions. Projections to the hippocampus, amygdala, basal ganglia, and autonomic control nuclei in the hypothalamus and periaqueductal grey probably convey its top–down bias. Inputs from the hippocampus provide information about navigation in an extrinsic coordinate frame, and inputs from the amygdala provide information about the current value of predicted outcomes.

Agranular cortex in primates

In the previous section, the evidence came exclusively from rats as representative rodents and, perhaps more controversially, as representative mammals. As explained in Chapters 1 and 2, all of the medial PF cortex in rats has an agranular cytoarchitecture, as it does in other mammals. In macaque monkeys, the anterior cingulate cortex (area 24) and the infralimbic cortex (area 25) are agranular, and the prelimbic cortex (area 32) ranges from agranular to dysgranular (Vogt & Derbyshire 2009; Mackey & Petrides 2010). The subgenual location of area 25 in monkeys, its cytoarchitecture, and its connections (Freedman et al. 2000) support its assignment as the homologue of the infralimbic cortex in rats, and

similar evidence supports the conclusion that the areas called anterior cingulate, infralimbic, and prelimbic cortex are homologous in rodents and primates (Chapter 2).

Action reversals

A critical experiment has assessed the ability of monkeys with medial PF lesions to switch between actions (Kennerley et al. 2006). On the action reversal task, monkeys face a choice among actions. First, they learn to perform one action, for example, lifting a handle consistently across trials. Later, they must learn to perform another action, for example, turning the handle consistently across trials. A series of further reversals then follows. For each reversal, a monkey needs to change its choice of action in order to produce a reward. The term contingency is often used to refer to the relationship between an action and its outcome. On the action reversal task, a monkey performs two different actions on the same object (the handle). Thus no external cues prompt the appropriate choice. Nevertheless, we note that the monkey performs its action on an object.

Kennerley et al. made lesions in the anterior cingulate cortex (area 24), including the rostral cingulate motor area (CMAr). They found that monkeys with lesions of the cortex in the cingulate sulcus switched between the two actions more slowly than normal monkeys (Figure 3.8).

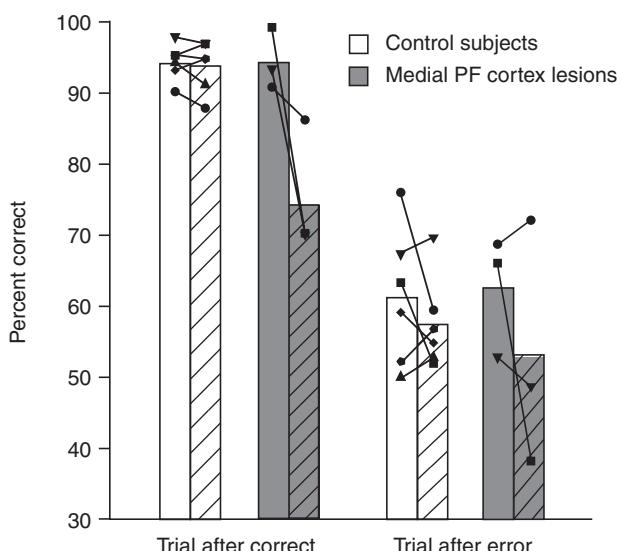


Fig. 3.8 Reversal impairment for choices among actions. Preoperative (solid bars) and postoperative (hatched bars) data from macaque monkeys. Percent correct after a correct choice (left set of four bars) and after an incorrect choice (right set of four bars), for normal (control) monkeys (white) and lesioned monkeys (grey). Results from individual monkeys are shown by the symbols and connected by lines. Medial PF lesions involved cortex in the anterior cingulate sulcus from the rostral limit of the sulcus to the rostrocaudal level of the precentral sulcus. Note that the lesioned monkeys have a larger and more consistent impairment on the choices made after correct trials. Reprinted by permission from Macmillan Publishers Ltd. Kennerley SW, Walton ME, Behrens TEJ, Buckley MJ, Matthew F, Rushworth S. Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience* 9:940–7, © 2006 Nature Publishing Group.

Importantly, this impairment did not result from perseverating with the previous action. In a key methodological advance, Kennerley et al. analysed their monkeys' behaviour trial-by-trial, rather than averaged over block of trials as psychologists have traditionally done. This procedure allowed them to observe that the animals showed an inefficiency in guiding their actions by the positive feedback provided by a reward as well as by the negative feedback provided by the lack of a reward. The perseveration account of the deficit predicts that problems in using negative feedback should play a larger role than problems in using positive feedback. The results did not confirm that prediction. In fact, the impairment could be characterized as a severe lack of persistence: the opposite of perseveration. Compared to control animals, those with anterior cingulate lesions persisted less with the correct option even after more than five rewards for that action. The anterior cingulate cortex of monkeys thus seems to promote the persistence of beneficial choices based on positive feedback, especially after a change in action–outcome contingencies induces monkeys to switch their choice of action.

Behrens et al. (2007) argued that the optimal strategy on such a task depends on the frequency of the reversals, which they related to the 'volatility' of resource availability in natural foraging. We said earlier that the prelimbic cortex of rats biases behaviour in way that is advantageous in moderately volatile situations. If a given condition prevails for many trials, a high probability of reward, for example, it does not pay to switch immediately to a new strategy because of a single failure.

Behrens et al. scanned human subjects while they switched between the choice of a blue or green square, both of which was associated with a particular probability and magnitude of reward. Thus this experiment involved a choice between stimuli rather than a choice between actions. It nevertheless led to activations in the medial PF cortex, an issue that we revisit later. Behrens et al. looked for an activation that covaried with a computational model in which the subject assesses the volatility of resources. The model was Bayesian, meaning that it uses prior knowledge about probabilities to evaluate hypotheses about the world. Bayesian reasoning supports a hypothesis when, given some event, that event is likely if the hypothesis is true but unlikely if the hypothesis is false. In the experiment by Behrens et al. the subject's hypotheses became wrong because of volatility in rewards. Behrens et al. found choice-related activation in the anterior cingulate cortex. The peak activation occurred in the cingulate sulcus and in the overlying preSMA. Activation related to monitoring outcome volatility, however, occurred in the medial PF cortex, specifically in the pregenual prelimbic cortex (area 32).

Behrens et al. studied choices between objects, whereas Kennerley et al. studied choices between actions. Rudebeck et al. (2008) specifically compared the effects of PF cortex lesions on learning object–outcome and action–outcome associations. They made lesions in both the orbital PF cortex and the medial PF cortex (more specifically, the anterior cingulate cortex in the banks of the cingulate gyrus). Chapter 4 takes up the orbital PF cortex, and we compare orbital and medial PF cortex there. For now we focus on the medial PF cortex. Rudebeck et al. found that lesions of the anterior cingulate cortex caused a deficit in action-based learning, not in object-based learning. Thus their data support the conclusion that the medial PF cortex of monkeys plays an important role in choosing actions based on action–outcome associations.

Glascher et al. (2009) used imaging to support the same conclusion for human subjects. The subjects were required to move a computer mouse in one of two ways. When the subjects switched between two actions, activation occurred in the anterior cingulate cortex.

This chapter is about the medial PF cortex, but we know that it does not function in a vacuum. In primates, it seems to function in close cooperation with the medial *premotor* areas that lie caudal to it, such as the preSMA and the SMA. Like lesions of the anterior cingulate cortex (Kennerley et al. 2006), lesions of the preSMA and SMA cause a deficit on the action reversal task (Chen et al. 1995). And in a different task involving associations between actions and outcomes, Thaler et al. (1995) showed that monkeys with lesions of either the anterior cingulate cortex or of the preSMA and SMA (together) showed impairments in reaching upwards to break an invisible infrared light beam. In this simple task, the internal representation of the outcome (a peanut) served as a prompt for the action, which the monkey performed in total darkness. Thus both anterior cingulate and premotor cortex lesions cause impairments on ‘internally’ guided actions. This similarity suggests that the agranular parts of the medial PF cortex affect the choice of action through its connections with the medial premotor areas.

Representations of value

Neurophysiological studies in monkeys demonstrate that cells in the medial PF cortex encode various outcome variables. Kennerley et al. (2009) recorded the activity of cells in the medial and orbital PF cortex. In their task, monkeys learned mappings between object-like visual stimuli and either probability of reward, the magnitude of reward, or the number of key presses required to gain the reward. The monkeys then chose between two of the stimuli, and they nearly always chose the stimulus associated with the higher benefit or the lower cost. The authors sampled cell activity in the medial PF cortex and in the orbital PF cortex, among other areas, searching for correlations in activity rates with one or more of the three valuation variables.

Based on the lesion results mentioned earlier, Kennerley et al. expected that the orbital PF cortex would most prominently encode stimulus–outcome associations, with the medial PF cortex more robustly encoding the effort parameter because of its relationship with action–outcome associations. And cells in the orbital PF cortex, as expected, encode stimulus–outcome valuations (Chapter 4). But cells in the medial PF cortex also showed activity of this sort, including activity that was related to all three decision variables: the size of the reward, the probability of the reward, and the number of key presses needed to get it. Other investigations of the anterior cingulate cortex (area 24) have found similar outcome-related signals (Seo & Lee 2007; Hayden & Platt 2010). Recall that in the imaging experiment by Behrens et al. (2007), activations in the medial PF cortex reflected a choice between stimuli.

We can interpret these findings in several ways. From one perspective, they agree with the attribution of action–outcome associations with the medial PF cortex. The activity related to analysing effort costs occurs in the medial PF cortex, as expected. One can also interpret these results in terms of decisions, choices, and actions, as distinguished earlier. Recall that decisions, in this sense, reflect the sensory world and not either

choices or actions (Schall 1991). Using this terminology, we can suggest that the medial PF cortex maps decisions to actions directly and that the orbital PF cortex maps decisions to actions indirectly through choices among objects. We pick up this discussion again in Chapter 4.

To understand the neurophysiological findings more fully, we would like to know whether the data come from the granular or agranular parts of the medial PF cortex. The lesions in the study by Kennerley et al. (2006) extended from the rostral tip of the cingulate sulcus to nearly as far caudally as the area 4/6 boundary (see Figure 1.2). So we do not know which part of this lesion caused the impairment on action–outcome learning. Without this knowledge, we cannot identify the critical area in cytoarchitectonic terms. The neurophysiological data could help, but unfortunately neither Kennerley et al. (2009) nor the other investigators who reported similar results (Seo & Lee 2007; Hayden et al. 2011b) have described the cytoarchitecture of their recording sites.

Kennerley et al. did, however, show an abrupt fall-off in value coding in the caudal part of their recording zone, in the dorsal bank of the cingulate sulcus caudal to the genu of the corpus callosum. This drop-off in value coding corresponded to an increase in the coding of actions. Hayden et al. also found value coding rostral to the genu of the corpus callosum. It is tempting to suggest that the rostral half of their recording zone corresponds to area 9 (granular cortex), especially for the dorsal bank of the cingulate sulcus. But the map of Carmichael and Price (Figure 2.1B) designates this area as part of area 24 in monkeys, and so we treat it as agranular cortex here. In human subjects, the cingulate activations for value seems to extend rostrally into the region variously called area 32ac (Öngür et al. 2003), area 32' (Vogt 2009), or cluster 3 (Beckmann et al. 2009).

In addition to encoding the value of outcomes, cells in the anterior cingulate cortex encode the difference between the expected outcome and the outcome that occurred. In Chapter 8, we discuss a reward-prediction error signal, which could lead both to the reinforcement of a behaviour and to its extinction, depending on the sign of the difference. By contrast, the error signal in the anterior cingulate cortex does not differ for underestimations and overestimations of an outcome (Hayden et al. 2011a). This unsigned error signal indicates only that the outcome did not occur as expected and that some adjustment in behaviour is in order. It signals little about what that adjustment should be. Nevertheless, this neural signal reflects a role in monitoring outcomes, and it probably contributes to the choice between staying with a given course of action and switching to some alternative.

A cell recording study by Hayden et al. (2011b) provides support for this idea. We have already mentioned this pioneering study. It incorporated two factors central to this chapter: the foraging decisions that primates face in the wild and the accumulator networks explained earlier. Hayden et al. found cells that encoded the value of switching from a diminishing resource to a new one. Whenever monkeys had to choose between exploiting a current but declining resource and switching to a new one, cells in the anterior cingulate cortex increased their activity. The monkeys also received a visual signal that informed them of how long it would take to begin exploiting the new resource, which Hayden et al. likened to the time it takes to travel from one patch of food to another, for example. For

each delay interval, activity climbed toward a fixed threshold that correlated with the choice to switch to the new resource, as predicted by accumulator–racetrack models. Longer delays increased this threshold and thereby implemented the delay-discounting function observed in many animals.

As in the studies by Kennerley et al. and others (Matsumoto et al. 2003; Seo & Lee 2007), Hayden et al. observed many cells in the anterior cingulate cortex that encode the value of rewards (Hayden et al. 2009; Hayden & Platt 2010). This result seems inconsistent with a role in implementing stay–shift choices. To reconcile these two findings, Hayden et al. (2011b) suggested that in all of these studies cingulate cortex cells encoded the likelihood that monkeys would use new information about resources to make a choice. And in all cases this choice involved a change from the ongoing exploitation of a resource to the exploration of a new one.

Likewise, Quilodran et al. (2008) showed that cells in the anterior cingulate cortex encode the feedback needed to switch between periods of exploration and exploitation. The activity signalled the first reward at the end of a period of exploration, and these cells ceased to encode rewards during periods of exploitation. At the beginning of new exploratory periods, the activity resumed.

An imaging study in human subjects supports the idea that the anterior cingulate cortex monitors outcomes in order to choose an advantageous action. Walton et al. (2004) showed that when subjects made their own choices of action, activation increased in the dorsal anterior cingulate cortex, but when experimenters chose the action, activation in the same area decreased. Thus the anterior cingulate cortex seems to play a role in monitoring self-generated actions, an idea we return to later when we discuss the polar PF cortex. The same investigators also showed that activation occurred in the anterior cingulate cortex when the outcome provided feedback information, irrespective of whether the outcome was positive or negative. In previous studies, which had suggested a role in error monitoring, it was the errors alone that provided feedback (Yeung et al. 2004). The findings of Walton et al. show that the function of the medial PF cortex is more general than error detection or conflict resolution.

Comparing rodents and primates

Chapter 2 explains that rats lack homologues of the granular PF cortex. Thus, we see the agranular parts of the medial PF cortex in primates as corresponding to the entire medial PF cortex in rodents. Accordingly, we have discussed the agranular PF cortex in both rodents and primates in the previous two main sections. However, others see the matter differently. Where their views relate directly to the medial PF cortex, we mention them briefly here. Later, Chapter 10 takes up the issue of species comparisons more generally.

Uylings et al. (2003) and Seamans and Durstewitz (2008) have proposed that the medial PF cortex in rats is homologous with the mid-lateral PF cortex (area 46), despite the fact that the former areas have an agranular cytoarchitecture and the latter has a granular architecture. In support of their conclusion, they have argued that the medial PF cortex in rats shares many properties with the granular PF cortex in monkeys, among which they

include impairments after lesions on spatial memory tasks and some properties of cell activity.

But these properties say nothing about homologies because they apply widely within the frontal cortex, granular and agranular areas included. Chapter 2 explains that diagnostic features distinguish one area from others, and the more such features, the stronger the conclusions. Traits in common to all of the areas in question provide no guidance about homologies. For this reason, neither the lesion effects nor the other properties support the homology of the medial PF cortex in rodents with any part of the granular PF cortex in primates.

We know that lesions of the medial PF cortex cause an impairment on the delayed response task in rats (Kolb et al. 1974). But so do lesions of the anterior cingulate cortex and prelimbic cortex in monkeys (Meunier et al. 1997), and similar lesions cause impairments on the delayed alternation task (Rushworth et al. 2003). In view of these findings, the impairment in rats provides no diagnostic evidence that the medial PF cortex in rats is homologous with the mid-lateral PF cortex in monkeys.

The impairments in both rats and monkeys might have some implications about analogies, as opposed to homologies (Brown & Bowman 2002). However, spatial information processing encompasses a broad range of functions, including navigation, reaching, place discrimination, distance discrimination, and so forth. One would have to argue that a task serves as a pure test of one of these functions in order to make a cogent case for an analogy between the medial PF cortex of rats and the mid-lateral PF cortex in monkeys. No one has yet formulated an effective argument along these lines.

Summary

In both rats and monkeys, the agranular medial PF cortex seems to play a role in the choice of actions based on predicted outcomes. Based on the linkage between actions and outcomes, animals can choose among specific actions. They can also choose to continue doing what they have been doing or switch to something else. The medial PF cortex contributes to both kinds of choices. Thus it does not merely link actions to outcomes in order to influence how frequently to make a specific action, how much effort to expend, or what action to make based on expectations about reward magnitude or probability. It performs these functions, but in addition it contributes choosing either an abstract action (exploit or explore) or a specific one. And it does so in either intrinsic or extrinsic coordinates. The latter occurs when animals choose a place as the goal of action; the former occurs when they choose an action directly. When outcomes meet expectations reliably, some parts of the medial PF cortex bias behaviour toward actions made without respect to predicted outcome (habits); when outcomes meet expectations less often, other parts of the medial PF cortex bias behaviour toward actions based on predicted outcomes.

Granular cortex

If we accept these conclusions, we still need to say how the granular parts of the medial PF cortex in monkeys differ from its agranular parts. Area 10 corresponds to the polar PF

cortex, and the medial part of area 9 corresponds to the dorsomedial PF cortex. Both have a granular cytoarchitecture, and Chapter 2 reviews the evidence that they evolved in anthropoid primates. Note that we reserve the term anterior cingulate cortex for agranular areas, so nothing that we have said so far about the anterior cingulate cortex refers to either of these granular areas.

To start with, we acknowledge a paucity of data. Except for imaging findings in human subjects, few experiments have addressed the functions of the medial part of area 9 or area 10 in primates. Looking to the rat literature provides no guidance because, as Chapter 2 explains, rats lack any homologues of these granular PF areas. Accordingly, the remainder of this chapter depends on less data than we would like.

As always, we look for clues from the connectional anatomy. On this basis, we suggest that the medial granular areas elaborate the functions of the agranular parts of the medial PF cortex. All of the medial areas receive predominantly ‘internal’ inputs and have a paucity of external ones, as explained earlier in the section on connections. We think that they all generate and bias the choice of action or a rule concerning actions when the available external cues do not indicate what action to make. In that situation, the choice of action depends on the value of a predicted outcome in the absence of external prompts. We propose that the granular parts of the medial PF cortex extend these functions.

Task rules

A study by Desmet et al. (2011) helps to illuminate the distinction between rostral and caudal parts of the medial PF cortex. When reward feedback informed human subjects about which *action* they should make, activation occurred caudally in the medial PF cortex, in the anterior cingulate cortex. When reward feedback informed subjects about which *task* to perform, rather than what specific action to take, a more rostral part of the medial PF cortex became activated. Venkatraman et al. (2009) obtained similar results. These findings suggest that rostral parts of the medial PF cortex contribute to choices between two tasks and that they influence specific actions via more caudal parts of the medial PF cortex.

In monkeys, lesions of the polar PF cortex (area 10) caused improvements in task performance when monkeys needed to resolve a conflict between two rules (M. J. Buckley, personal communication). Furthermore, lesioned monkeys, but not normal ones, successfully returned to an ongoing primary task after engaging in a secondary task or after the delivery of unexpected rewards between trials. Like the imaging result just mentioned, these findings point to a role for the most rostral PF cortex in influencing the bias between two task rules. Chapter 9 picks up this discussion for human subjects.

Self-generated goals

The only neurophysiological findings on medial 9 in monkeys come from a study by Tsujimoto et al. (2006). These investigators measured theta oscillations in medial areas 9 and 32. Theta waves are electrical potentials with a frequency of 4–7 Hz. Tsujimoto et al. reported three findings: (1) an increase in the power of the theta oscillations that occurred before monkeys made self-initiated movements; (2) a similar increase in power at the

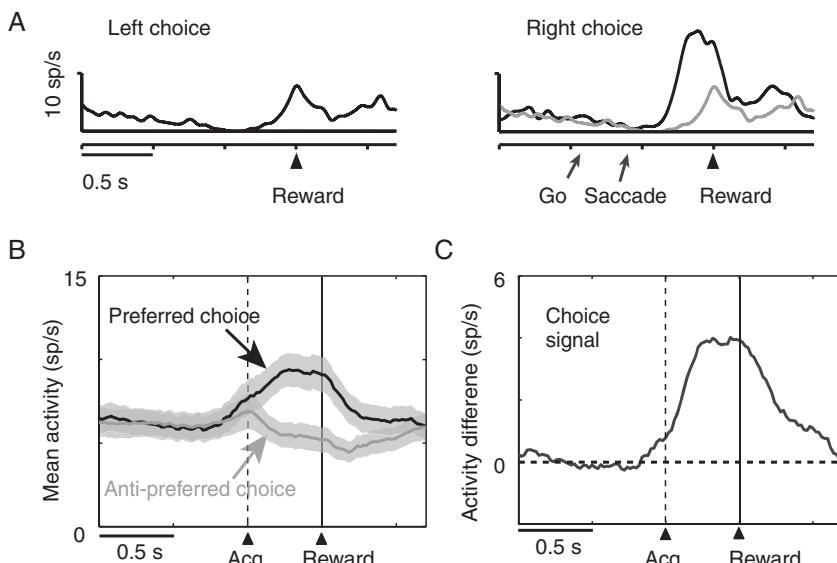


Fig. 3.9 Cell activity encoding choices at feedback time in the polar PF cortex (area 10). (A) Activity from a cell encoding the rightward goal choice at the time of reward (right). The activity for left choice is replicated in grey in the plot at the right. (B) Population activity for each cell's preferred choice (black) and the alternative (anti-preferred) choice (grey). Abbreviation: acq, acquisition of goal. Shading: SEM. (C) Choice signal expressed as the difference between the curves in (B). Data from Tsujimoto S, Genovesio A, Wise SP. Evaluating self-generated decisions in frontal pole cortex of monkeys, *Nature Neuroscience* 13:120–126 © 2010.

time of reward; and (3) oscillatory coherence between the two areas. Theta oscillations could organize the information represented in the cortex, and the findings regarding self-generated goals around the time of reward presage those explained next, from the polar PF cortex (area 10).

Another neuroscientist named Tsujimoto studied neuronal activity in the polar PF cortex (area 10) while monkeys performed a visually cued strategy task (Tsujimoto et al. 2010). On each trial, a cue instructed the monkey to make a saccade in the same direction as on the previous trial ('stay' cues) or to make a saccade in the opposite direction ('shift' cues). As illustrated in Figure 3.9, Tsujimoto et al. found that neurons in the polar PF cortex encoded the goal that the monkeys had chosen on each correctly executed trial and that they did so only around the time of the feedback (the outcome).

Note that the cues did not directly specify the direction of the saccade or its goal. The cues simply told the animal to stay with its most recent successful goal or to shift to the alternative goal. The monkey had to use its memory of the previous goal to choose the next one. In other words, although the stay and shift cues were external, the monkey had to generate the goal on the basis of internal signals.

In the same experiment, Tsujimoto et al. included a condition in which spatial cues instructed the animals about which goal to choose on each trial: the oculomotor delayed

response task. They compared activity when feedback occurred at the usual time with activity for later-than-usual feedback. In the latter case, the neuronal signal did not persist until the feedback arrived. By contrast, in the cued-strategy task, the cells continued to encode the chosen spatial goal for several hundred milliseconds after the feedback in all cases. Tsujimoto et al. interpreted this finding as indicating that the polar PF cortex plays an important role in evaluating self-generated goals, as opposed to the purely externally instructed ones in the oculomotor delayed response task. The finding that all of the goal encoding occurred at the time of the outcome indicates that the polar PF cortex plays a role in the choice of future goals rather than in the selection of goals during an ongoing trial.

Tsujimoto et al. also compared activity during error trials with that on correct trials. They assumed that on correct trials the monkey generated a goal based on the cued strategy ('stay' or 'shift') and that on error trials the monkey generated the goal on some other basis. In contrast to robust goal encoding on correct trials, the same neurons barely encoded the goal on error trials, if they did so at all. This finding shows that the polar PF cortex encoded goals generated on the basis of the cued strategy, which required the conjunction of an external cue and the memory of the most recent prior goal. When the monkey chose a goal on some other basis, the polar PF cortex encoded the goal weakly, if at all.

In the next chapter, we suggest that the granular PF cortex allows monkeys to link single events with outcomes, and we contrast this learning with the slow adjustment of associations over many trials. The representation of the chosen goal around the time that the outcome occurs probably contributes to learning these linkages.

Single events

Other evidence also points to the importance of single feedback events. A task devised by Gaffan (1992), called the object-in-place scenes task, allows an investigation of event-based learning. The monkeys see a series of coloured, complex background scenes, and each scene contains two coloured shapes (letters) that always appear in the same place within their particular scene. The monkey needs to learn which coloured shape to choose in order to receive a reward.

Monkeys learn this task very rapidly, even though they see a series of 20 scenes before any scene repeats. This fast learning probably depends on the ability of monkeys to embed their memory of touching a particular coloured shape in a specific context, which consists of a particular background scene. The conjunction of a goal (the coloured shape), an action (touching it), a context (background scene), and an outcome (reward) composes an event.

Piekema et al. (2009) gave this task to monkeys with lesions of the polar PF cortex (area 10). These lesions caused severe impairments on the second presentation of each scene, but the monkeys resumed a fairly normal rate of learning thereafter (Figure 3.10). Of course, control monkeys have less room for improvement after the second presentation than do the lesioned ones. So all we can say is that learning rates seem generally comparable after the second presentation. The key point is that the second presentation

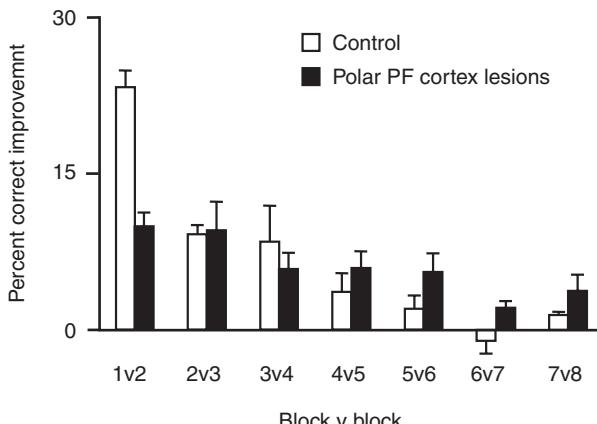


Fig. 3.10 Impairment on trial two in the objects-in-place scenes task after lesions of the polar PF cortex (area 10). Each bar shows the difference, in terms of the percentage of correct choices, for successive blocks of trials, for normal (control) monkeys (white) and lesioned monkeys (black). Each choice appears once in a 'block' of 20 choices. Abbreviation: v, versus. Data from Piekema et al. (2009), courtesy of Dr Mark J. Buckley.

of each scene assesses the ability of the monkeys to remember single events, which consist of their initial choice for each of the 20 scenes, and recall them from long-term memory. Chapter 8 argues that this finding does a lot to explain the PF cortex.

Event memory

In cognitive psychology, the term episodic memory refers to recollection of single events. We avoid that term for studies of monkeys because it implies awareness of the event. In humans, however, it is often easy to assess awareness. Experimenters can simply ask subjects to recall events from their life, called autobiographical memories. So, for example, Hassabis et al. (2007a) asked subjects to remember things that they had done, such as buying a ticket at a cinema booth. Such events comprise conjunctions of actions, goals, contexts, and outcomes at a particular time and place. Hassabis et al. then contrasted the subjects' memory for actions of this sort with the memory for objects. Differential activation occurred for the two kinds of memory—event memory and object memory—in the medial PF cortex (area 9), as well as in the retrosplenial cortex and in the hippocampus. Similarly, Summerfield et al. (2009) scanned subjects while they retrieved different sorts of events from episodic memory. They found activation in the medial part of the polar PF cortex (area 10), as well as in the retrosplenial cortex and in the hippocampus.

Summary

Monkeys with lesions of the polar PF cortex (area 10) have impairments on the second trial of the object-in-place scenes task; cells in the polar PF cortex encode self-generated goals at the time of feedback; and human subjects have activations in the polar PF cortex (medial area 10) and in medial area 9 when they retrieve the memory of single autobiographical events and when they choose among task rules. The impairment in the

object-in-place scenes task might reflect either a failure to retrieve the relevant event from long-term memory or a failure to use that memory to influence the current goal choice. The background scene provides a current context, and the correct choice on trial two depends on one-trial learning from a single autobiographical event.

Earlier, we argue that the *agranular* parts of the medial PF cortex generate biases among actions or rules based on actions. These biases depend on ‘internal’ signals that involve motivational states and the memory of previous events, including actions and outcomes. In this section, we propose that the *granular* parts of the medial PF cortex elaborate the functions of the agranular parts. Both use primarily ‘internal’ signals to guide choices. Sometimes these choices involve actions performed on objects and sometimes they involve actions per se. The granular areas elaborate the function of the agranular ones by generating goals or rules ‘internally’ and by implementing a mechanism for one-trial learning, that is, learning based on a single event. Part of its mechanism involves the representation of chosen goals around the time of feedback and the subsequent retrieval of this event from long-term memory.

Conclusions

How the medial PF cortex can do what it does

The connections of the medial PF cortex with the hippocampus, amygdala, and medial premotor areas explain its contributions to the PF cortex, as a whole:

1. The medial PF cortex has strong reciprocal connections with the hippocampal system, both directly and indirectly via the retrosplenial cortex, entorhinal cortex, and thalamus. Because of the role of the hippocampus in guiding navigation in an extrinsic (allocentric) coordinate frame, a bias toward extrinsic-guidance rules should occur when the hippocampus controls behaviour. There is evidence that parts of the basal ganglia control behaviour when rules based on intrinsic guidance predominate (Packard & McGaugh 1996). The medial PF cortex, in particular its prelimbic and infralimbic areas, provides a top-down bias toward one or the other rule. More generally, this top-down bias provides a mechanism via which the medial PF cortex can exert attentive control, and in Chapter 8 we argue that the PF cortex as a whole exerts such control.

Connections with the hippocampal system also provide to the medial PF cortex information about navigation and other action-related events, and in Chapter 9, on the human PF cortex, we propose that navigation and event information serves to embed one’s own actions within the representation of an event.

2. The connections of the medial PF areas with the amygdala explain how these areas associate actions with the current value of outcomes. As animals consume a fluid or a nutrient, their needs change and the interaction between the amygdala and the PF cortex updates the valuation of behavioural outcomes that involve these resources. Similar updating probably occurs for negative outcomes, such as effort costs, the harmful results of action, and fear-inducing stimuli. These evaluations bias the choices among actions associated with those outcomes.

When an expected value fails to materialize, animals need to switch their actions, and the medial PF cortex promotes the efficient use of reward feedback to perform such reversals of action, including a switch between exploiting a diminishing resource and leaving it to explore a new one.

3. The connections with medial premotor areas allow the medial PF cortex to influence motor commands.

Although these three sets of connections tend to concentrate in the caudal, agranular part of the medial PF cortex, strong connections between the agranular and granular areas enable the medial PF cortex, as a whole, to use them. Chapter 9 discusses the hierarchy within the medial PF cortex of humans (see Figure 9.7).

Proposal

In Chapter 8, we advance a proposal about the fundamental function of the PF cortex as a whole. Each region contributes to that function, and so we begin the development of our proposal with a statement about the medial PF cortex, first in its briefest form and then in an expanded version.

In brief:

The medial PF cortex contributes to evaluating and choosing among actions based on associations with outcomes, in relation to current needs.

Expanded:

The medial PF cortex contributes to the function of the PF cortex, as a whole, by biasing the choices among actions and rules based on actions. It does so via an evaluation of the expected outcomes, as assessed in terms of current needs. When outcomes fail to meet current needs, the medial PF cortex promotes the efficient use of this feedback to switch between exploiting a diminishing resource and exploring a new one, to switch between alternative actions, to switch between competing action rules, and to switch between competing behavioural control systems. In primates, it can do so based on single events.

Why other areas cannot do what the medial PF cortex does

Other areas cannot do what the medial PF cortex does because they lack one or more of its key connections. Many of the other parts of the PF cortex lack its hippocampal connections. The posterior parietal cortex has direct connections with the premotor areas of cortex, like the medial PF cortex, but lacks those from the amygdala, at least to any appreciable extent (Figure 3.3). The same constraint applies to many other parts of the cerebral cortex. The superior and inferior temporal cortex have connections with the amygdala—the visual areas more so—but lack direct connections with the premotor areas that the medial PF cortex has.

Contribution to foraging choices

The medial PF cortex helps animals choose among competing actions. In many cases, no external cue prompts the animal at the time of choice. The animal can see (or otherwise

sense) many stimuli, but none of them provide the basis for choosing one action over another. In that situation, only the association of an action with its outcome enables animals to choose among actions. During foraging, animals often need to choose among potential actions without any external prompts to guide those choices. Cues abound in the natural environment, of course, but they often fail to provide guidance about what to do. In that circumstance, action–outcome mappings provide the requisite guidance.

Cells in the medial PF cortex encode outcomes in terms of quantity, probability of occurrence, and effort costs, and all of these factors enter into foraging choices. As a result, the agranular medial PF cortex can bias the competition among competing actions, competing coordinate frames, and different kinds of associations, all of which could lead to success in certain circumstances. For example, one part of the medial PF cortex exerts a bias toward outcome-directed behaviour when, due to increased resource volatility, habitual foraging choices become less effective. And another part generates the opposite bias, promoting fast, automatic behaviour in stable foraging environments.

The granular parts of the medial PF cortex make an additional contribution to foraging choices in anthropoid primates. We have only a few clues about their function: activation occurs in the medial part of area 9 or the polar PF cortex (area 10) when people recollect autobiographical events or generate task rules; cells in the polar PF cortex of monkeys encode self-generated goals at feedback time; and lesions of polar PF cortex impair the ability of monkeys to use single events to choose future goals. These findings point to a role in assigning outcomes to goals, in order to improve future choices (Tsujimoto et al. 2011b).

The concept of an event is important to these conclusions. By *event* we mean the conjunction of a context, a goal choice, an action, and an outcome at a particular time and place. Making foraging choices based on a single prior event could provide advantages in the pursuit of highly volatile resources, as anthropoid primates face (Chapter 2). Chapters 4–7 take up the idea that single events play a major role in the function of the granular PF cortex, and Chapter 8 argues that the capacity to use single events to choose goals is central to the fundamental function of the prefrontal cortex.

This chapter reviews evidence that the medial PF cortex contributes to choosing actions based on their association with outcomes of value. Animals can choose actions directly or indirectly via choices among objects. We argue that the connections of the medial PF cortex allow it to function in the choice among actions, especially when those choices occur in the absence of external sensory signals that tell an animal what to do. The next chapter addresses the orbital PF cortex, its role in choices among objects, and why the medial and orbital PF cortex must interact.

Chapter 4

Orbital prefrontal cortex: choosing objects based on outcomes

Overview

The orbital PF cortex contributes to evaluating and choosing objects as goals for future actions, and its connections explain its unique functions. It has connections with the olfactory, visceral, gustatory, somatosensory, and visual areas of cortex, and the conjunction of these signals generates a rich, high-dimensional representation of specific outcomes, one dominated by vision. The interaction of the orbital PF cortex with the amygdala updates the valuation of these outcomes in terms of current biological needs. Because of these connections, the sight of nutritious foods or visual signs associated with them evokes their flavour and their current motivational value. While a large part of the orbital PF cortex links objects to specific outcomes, another part does so for outcomes in general, in a ‘common currency’. By assigning a behavioural outcome to a particular foraging event, rather than an average of such events, the orbital PF cortex of primates provides a key selective advantage.

Introduction

Chapter 3 argues that the connections of the medial PF cortex allow it to make choices among actions, especially when those choices occur in the absence of external sensory prompts that tell an animal what to do. This chapter addresses the orbital PF cortex. It argues that the connections of the orbital PF cortex allow it to do for externally prompted choices what the medial PF cortex does for ‘internally’ prompted ones.

Like the medial PF cortex, the orbital PF cortex has both agranular and granular parts. Chapter 2 argues that the agranular parts evolved in early mammals and that the granular parts evolved in early primates. As in Chapter 3, we need to draw upon evidence from rats for insight into the agranular ones. The reason is the same: we know relatively little about the agranular PF cortex in primates. Also like Chapter 3, we need to say what the granular parts of the orbital PF cortex can do that its agranular parts cannot. We adopt the idea that the orbital PF cortex in primates uses single events to link particular outcomes to the choices that caused those outcomes: a form of stimulus–outcome association.

Obviously, most animals can learn stimulus–outcome associations. Pavlovian conditioning depends on it, just as instrumental conditioning depends on learning action–outcome associations. Except for sessile forms, we assume that all animal species can be instrumentally and classically conditioned. So we face a challenge: we need to say what the agranular parts of the orbital PF cortex add in mammals and what the granular parts of the orbital PF cortex add in primates.

In this chapter, we distinguish two aspects of stimulus–outcome associations. The first involves the predictive relationship between a stimulus and an outcome: the likelihood that an outcome will occur given the stimulus. The second involves an assessment of that outcome’s value in terms of current biological needs. Both aspects, which we call *associative mappings* and *motivational valuations*, respectively, affect foraging choices, and both need to be updated as circumstances change.

Areas

Figure 4.1 illustrates the orbital PF cortex in humans and monkeys, and Figure 2.1 illustrates one view of its subdivisions. In macaque monkeys, area 11 lies in its rostral part, with areas 13 and 14 situated more caudally (Walker 1940). In primates, most of this cortex has a granular cytoarchitecture, but the caudal parts of areas 13 and 14 are agranular, as is the adjacent anterior insular cortex. Following Carmichael and Price (1994), we include all of these agranular areas in the orbital PF cortex. For clarity, we sometimes use the abbreviation OFC for the orbital PF cortex. We do this especially when discussing subdivisions of the OFC.

We exclude the parts of area 12/47 that extend onto the orbital surface of the hemisphere from the orbital PF cortex as construed here, along with the orbital parts of the polar PF cortex (area 10).

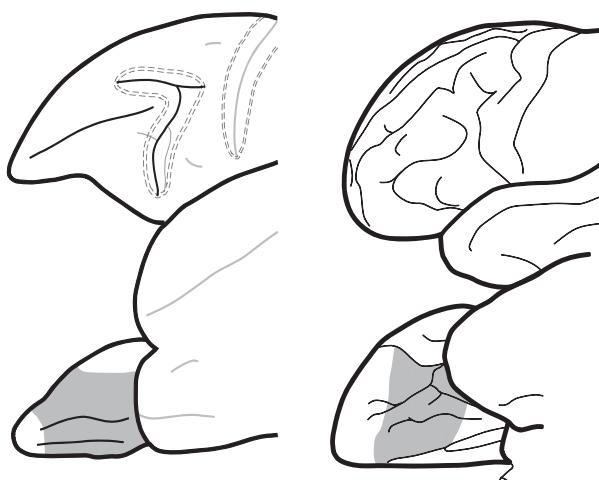


Fig. 4.1 The orbital PF cortex in monkeys (left) and humans (right). Format as in Figure 1.2.

Connections

Figure 4.2 illustrates the selected connections of the orbital PF cortex, which suggest the following conclusions:

1. The densest connections with the amygdala involve the agranular parts of the orbital PF cortex, which connect preferentially with the basolateral nuclei of the amygdala. However, the granular part of area 13 also has connections with the amygdala, as do other granular subdivisions (see Figure 3.3) (Carmichael & Price 1995a).

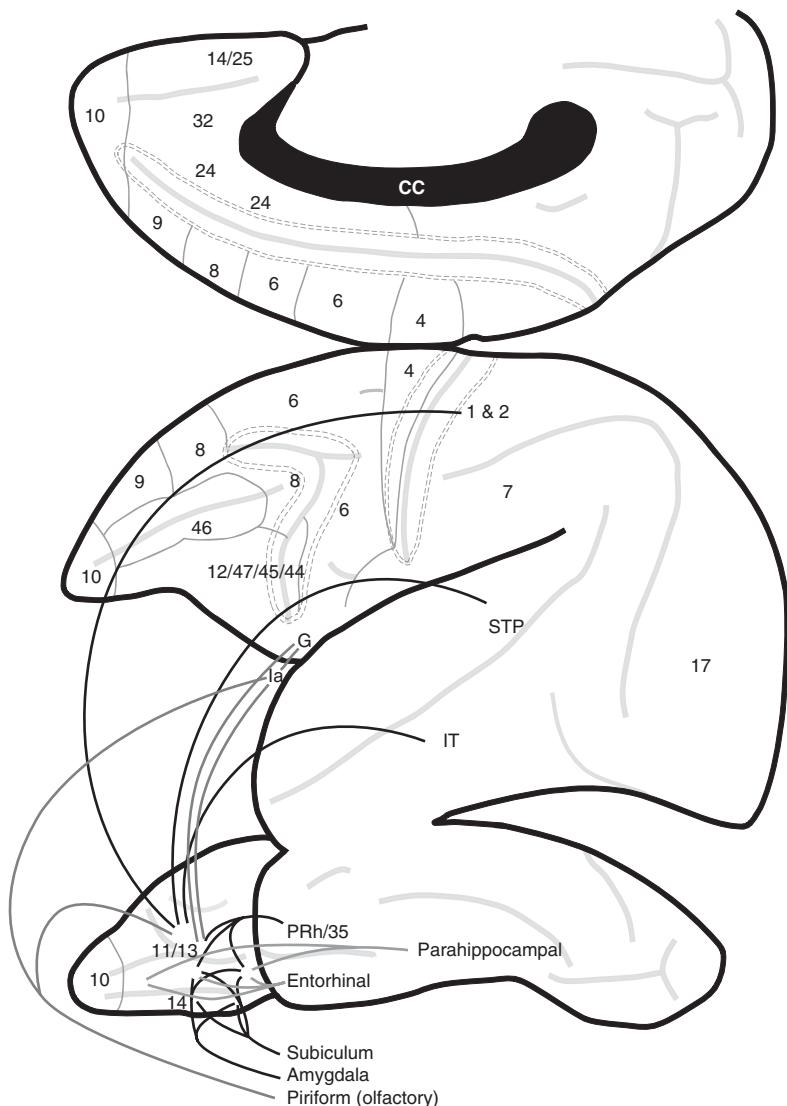


Fig. 4.2 Selected connections of the orbital PF cortex. Figures 1.4 and 1.5 give the names of sulci and areas. Lines connect some of the areas that have direct axonal connections with orbital areas, assumed to be reciprocal unless otherwise stated.

2. The agranular insular cortex receives relatively direct inputs from the gustatory and piriform (olfactory) cortex (Carmichael & Price 1995a). It also receives visceral signals from the brainstem and thalamus (Ray & Price 1992). The latter include sensations that convey signals that reflect an animal's metabolic state, for example, hypoxia or hypoglycaemia, and inputs from the lungs, heart, baroreceptors, and digestive tract (Craig 2002). These findings have led to the view that the agranular insular cortex functions in interoception.
3. Olfactory, gustatory, and visceral information arrives in the granular OFC from its agranular parts (Carmichael & Price 1994). This information can combine in granular cortex with visual inputs from the inferior temporal cortex, which target areas 13 and 11, and from the perirhinal cortex, which projects to area 13 (Saleem et al. 2008). The latter projection provides multimodal information about objects (Murray et al. 2007).
4. Somatosensory information from areas S1 and S2 also goes to area 13, especially those lateral parts that represent the mouth (Pritchard et al. 1986), lips, and tongue (Carmichael & Price 1994). These connections include ill-defined somatosensory areas such as those in the parietal operculum and the dysgranular parts of the insular cortex (Saleem et al. 2008), as well as well-defined somatosensory areas such as area 3b and S2 proper. Some connections with S2 could involve the hand as well as orofacial representations (Carmichael & Price 1994).
5. Unlike the medial PF cortex and the ventral PF cortex (Chapters 3 and 7), the orbital PF cortex has only a restricted auditory input (Saleem et al. 2008). Parts of area 14 and 13 have connections with areas in the temporal lobe that probably provide auditory inputs (Petrides & Pandya 1988). But Saleem et al. (2008) have reinterpreted these connections in terms of two connectional networks that they recognize: the orbital and medial networks. They argued that the areas with auditory connections were either part of the medial network or part of both networks. On this view, 'purely orbital' parts of the orbital PF cortex lack auditory inputs. The reason is probably that orbital network processes information about objects such as foods, which have few auditory features.

These points compose the connectional fingerprint of the orbital PF cortex, which suggests that it is the earliest site for the convergence of visual information with gustatory, olfactory, and visceral inputs. We take it as important that most of the visual inputs arrive in the granular areas, which are specific to primates. Thus it is not the orbital PF cortex, in general, but specifically the granular parts of areas 13 and 11 that appear to be the earliest sites for the convergence between visual, olfactory, gustatory, and visceral inputs.

Because of this convergence, the sight of a particular food, such as a fruit at a particular stage of ripeness, can evoke its taste and smell, which compose its flavour, along with the visceral sensations that follow its ingestion. Furthermore, the orbital PF cortex receives inputs from mouth, lip, and tongue representations of the primary somatosensory cortex (S1): the parts of the body most involved in the ingestion of foods and fluids (Carmichael & Price 1995b).

Its connectional anatomy puts the orbital PF cortex in a unique and interesting position. Tactile inputs provide signals about nearby parts of the external environment; visual and olfactory inputs convey signals from the distant parts of the outside world; visceral inputs tell the animal about its internal environment; and gustatory and oral somatosensory inputs inform it about things entering the internal world from the outside.

Figure 4.3 shows how these various modalities and submodalities could combine to form conjunctive representations. Some of these conjunctions occur in agranular areas, and they seem to be ideally suited to the grain and insect diets of early mammals. These were small animals that specialized in nocturnal foraging to avoid predation, among other factors. Accordingly, the conjunctions represented in the agranular parts of the orbital PF cortex involve predominantly taste, smell, and visceral sensations. Primates

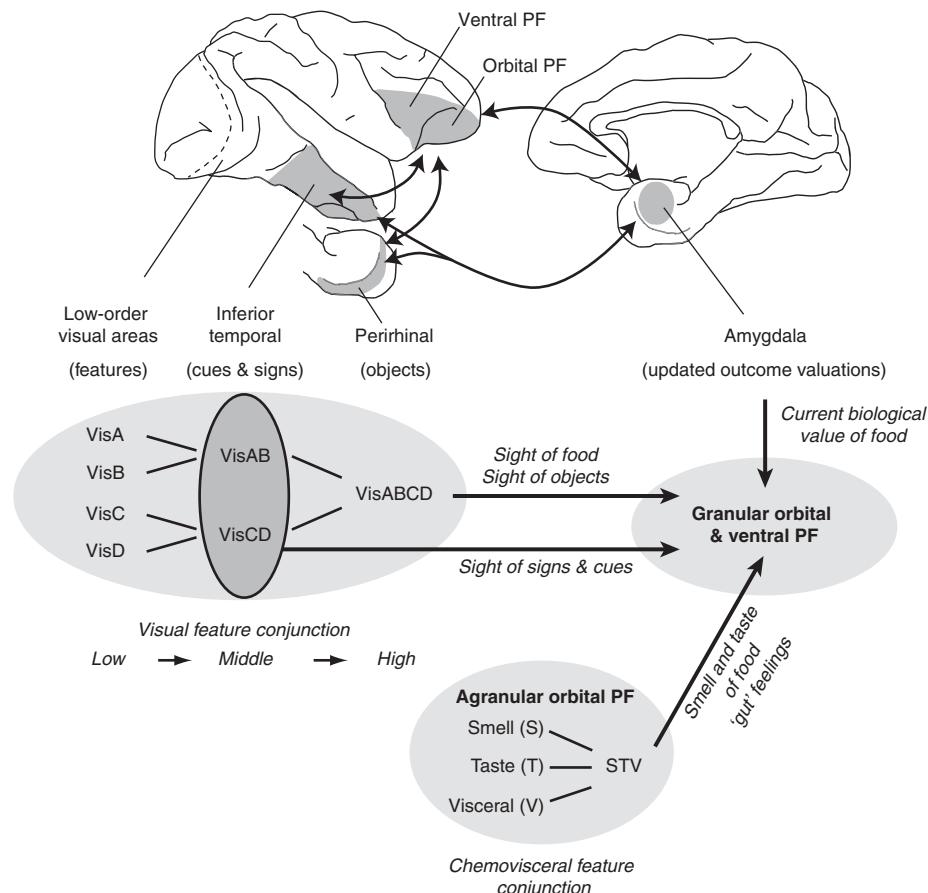


Fig. 4.3 Feature conjunctions in the temporal and frontal cortex. VisA ... VisD designate visual features of an object, which can combine in various conjunctive representations, such as VisAB, which indicates the representation of both VisA and VisB. 'STV' indicates a conjunction of an object's smell (S), taste (T), and visceral (V) properties. Reproduced from Murray EA, Wise SP, Rhodes SE, What can different brains do with reward? In *The Neurobiology of Sensation and Reward*, ed. JA Gottfried © 2011, Taylor and Francis, with permission.

have retained this basic feature-conjunction mechanism, with the addition of greater input from visual areas.

Summary

Chapter 3 argues that—through its connections with the hippocampus, amygdala, and medial premotor areas—the medial PF cortex biases the choices among actions or among rules concerning actions. There we reviewed evidence that it does so based on the current value of predicted outcomes, especially when these choices depend on ‘internal’ signals rather than sensory ones. This chapter takes the view that the orbital PF cortex performs a similar function for choices among external signals, especially those arising from objects. It can do so because of the convergence and integration of information from the somatosensory, gustatory, olfactory, visceral, and visual cortex and from the amygdala.

Agranular cortex in rodents

The agranular OFC has attracted considerable attention in rodent research, much of which points to an important role in outcome-directed behaviour. Recall that throughout the book we distinguish between goals and outcomes, and thus use the term outcome-directed where others might say goal-directed. The activity of OFC cells reflects outcome predictions, especially predictions about the specific sensory aspects of rewards (Schoenbaum et al. 1998), and lesions of these areas impair choices that are based on outcome expectations, as explained in the next section.

Stimulus–outcome associations

As Chapter 3 mentions, current biological needs influence the valuation of outcomes. The greater the current need, for food or fluid, for example, the greater the value of a stimulus that maps to that outcome. Consuming a food to satiety devalues that food, and there are other methods for varying the value of outcomes, as well.

In experiments that devalued food rewards with one of these alternative methods, Gallagher et al. (1999) compared the behaviour of rats with lesions of the agranular OFC to that of normal rats. First, they taught rats that a light signalled food availability. Rats then approached the light when it turned on. Then Gallagher et al. used lithium chloride to induce a gastrointestinal illness, a procedure called conditioned taste aversion. When tested later, after all trace of the illness had passed, normal rats approached the light less often than they had before the illness or ceased approaching it entirely. The lesioned rats behaved differently. They approached the light more often than did normal rats. As Chapter 3 explains, the result in normal rats is called the devaluation effect. Because the lesioned rats approached stimuli associated with a devalued reward, they can be said to have an impairment in using stimulus–outcome associations to guide action.

Pickens et al. (2003, 2005) used the same task and devaluation procedure but made lesions of the amygdala as well as of the agranular OFC. Both lesions abolished the devaluation effect in rats. These rats behaved as if they had learned nothing from their illness.

The results from these devaluation procedures resemble those that Chapter 3 describes for lesions of medial PF cortex. Medial PF cortex lesions cause impairments in using predictions about outcomes to choose among competing actions. In many of these experiments, no external prompt helps animals make the choices. Agranular OFC lesions, however, do not disrupt such action–outcome associations (Ostlund & Balleine 2007). Instead, they disrupt the use of predictions about outcome to choose among objects. In these experiments, an external cue prompts the choice and thus reveals impairments in learning stimulus–outcome associations. These studies show that the agranular OFC associates stimuli with outcomes, especially the sensory aspects of food such as its smell or taste.

An experiment by Burke et al. (2008) supports this conclusion. Rats first learned to associate one stimulus with a particular kind of food. Later they saw this stimulus combined with an additional stimulus. When the rats saw this compound stimulus, they learned that it was associated with a different kind of food. The two foods had more or less the same palatability and desirability, but they tasted different.

Burke et al. found that the rats attributed the occurrence of the second food to the newer part of the compound stimulus. As evidence for this conclusion, they showed that their rats would press a bar to produce the additional stimulus. Crucially, Burke et al. showed that the rats were less likely to do this if they had become satiated on the second food. Thus, the rats not only associated the additional stimulus with the second food, but used that association to assess the current value of the stimulus.

Rats with lesions of the agranular OFC failed to show these effects. The relationship between the newer part of the compound stimulus and the specific sensory properties of the second food no longer influenced their behaviour. These results suggest that the agranular OFC mediates mappings between stimuli and outcomes, and especially the specific sensory aspects of outcomes.

Later, we emphasize the importance of the granular OFC and the visual advances of primates. However, as the experiments just reviewed demonstrate, rats also use visual stimuli to assess outcomes, which their OFC receives from visual areas of cortex.

Costs

Chapter 3 explains that animals base decisions not only on predicted foods or fluids, but also on the costs of obtaining them. For example, rats with lesions of the anterior cingulate cortex choose to climb over a barrier less often than normal rats and so seem to overestimate effort costs.

Lesions of the agranular orbital PF cortex also change the way that rats estimate costs. When given a choice between a small immediate reward and a large delayed reward, normal rats take the length of the delay into account in making their choice. Rudebeck et al. (2006b) reported that rats with orbital PF lesions chose the small immediate reward more often than normal rats. The term ‘impulsive’ has been applied to choosing a small reward quickly, and the term ‘patience’ has been used for foregoing an immediate reward to get a larger one later. So in the experiment of Rudebeck et al., orbital PF cortex lesions can be said to induce impulsivity.

With slight changes in the experimental design, however, one can get a different result. Rudebeck et al. used a T-maze, but Winstanley et al. (2004) gave rats the choice between two levers, one leading to a single pellet and the other to four pellets after a delay. The rats with orbital PF lesions chose the lever with delayed reward more often than normal rats. One might say that they showed more ‘patience’ than normal. And Mariano et al. (2009) gave the rats a choice between a black or white goal box on a T-maze, with a small reward in one box, and a large reward in the other, which could only be gained after a delay. Again, rats with orbital PF lesions showed more ‘patience’ than those in the study by Rudebeck et al.

Zeeb et al. (2010) suggested that whether orbital PF lesions cause ‘impulsive’ or ‘patient’ choices depends on two factors: a clear cue that signals the delay and differences among individual rats. They inactivated the orbital PF cortex and compared the effect of cued and uncued delays. Their results showed that for clearly cued delays the inactivation increased the choice of the immediate reward (impulsivity), whereas for uncued delays the inactivation decreased the choice of the immediate reward (patience), but only in individual rats that have a strong tendency toward impulsivity.

So we cannot say simply that the rat orbital PF cortex biases choices toward impulsive or patient foraging. However, it clearly plays a role in assessing delay costs in some way and in biasing behaviour toward delayed or immediate actions. As Chapter 3 explains, accumulator–racetrack models provide a simple mechanism for implementing this bias, either by changing the threshold for producing an output or by modulating the rate at which ‘evidence’ in favour of making a particular movement accumulates.

The competition between impulsive and patient foraging is usually discussed in terms of devaluation or discounting of foods and fluids that are available at a delay or at a distance. However, as Stephens et al. (2004) have pointed out, this terminology implies that animals incorrectly assess the value of foods and fluids that are distant in time and space. Alternatively, the animals might assess the values accurately but take into account the risks inherent in seeking a distantly available resource.

Hayden and Platt (2007) have produced a model in which the valuation of a ‘risky’ option depends on the expected time of the larger payoff and the risk that the payoff would decrease. They showed that the predictions from this model accounted for the choices that monkeys made on a gambling task. Because of the risks inherent in waiting longer or going farther, the choice to exploit an immediately available resource does not necessarily imply an incorrect assessment of the delayed or more distant resource. Even if the immediate patch has less value than ‘greener pastures’ elsewhere, the payoff is more certain.

Agranular insular cortex

Based on connections, cytoarchitecture, and topology, the orbital PF cortex includes the agranular insular cortex (Carmichael & Price 1994). If the agranular orbital PF cortex associates stimuli with the specific sensory aspects of outcomes, we might expect to find a related function for the neighbouring agranular insular cortex.

Balleine and Dickinson (2000) showed that rats with lesions that included the agranular insular cortex show impairments when they need to remember specific tastes. They tested rats in two conditions. In one, rats chose between two levers and received the kind of food associated with either choice. The lesioned rats tended to avoid pressing the lever that had just led to a devalued reward. In a second condition, the bar presses no longer produced any food; that is, the rats were tested in extinction. In this condition, the lesioned rats pressed both levers equally.

Because other experiments show that rats with these lesions can learn extinction tasks of this kind, Balleine and Dickenson concluded that the lesioned rats could not recall the specific sensory properties of the food that they expect to receive by pressing each lever, and so chose them equally notwithstanding the devaluation of one of the foods. Although their lesions invaded the gustatory cortex, which lies caudal to the agranular insular cortex, the effect could have resulted from agranular insular cortex lesions.

Kesner and Gilbert (2007) also tested the ability of rats to anticipate reward. The rats had access to a low-sucrose fluid followed by a high-sucrose one, and over days they drank less of the low-sucrose fluid in order to consume more high-sucrose fluid later. Lesions in the agranular insular cortex abolished this effect. Yet control tests showed that the lesioned rats could still tell the difference between the two fluids. This experiment indicates that the rats with lesions in the agranular insular cortex tend to choose the immediate reward, rather than waiting for the higher value but delayed reward. This result could reflect a failure to anticipate the properties of the delayed reward or an impulsive choice.

Summary

Taking what this chapter says with Chapter 3, the agranular parts of the medial PF cortex seem to use *action*–outcome mappings and motivational valuations to bias a choice among actions or rules concerning actions. Both the mappings and valuations involve ‘internal’ signals, and both can influence activity in accumulator networks that represent particular choices (Chapter 3). So, for example, the ‘internal’ signal that pressing a lever predicts a beneficial outcome (such as a raisin) and the signal that assesses that outcome in terms of current needs both provide ‘evidence’ to accumulator networks that represent the act of bar pressing. With more of this ‘evidence’—a stronger association or a higher motivation to obtain a raisin, for example—the network will reach threshold faster and ‘win’ the ‘race’ to control behaviour.

By contrast, the agranular parts of the orbital PF cortex seem to use *stimulus*–outcome mappings along with motivational valuations to bias a choice among stimuli. Unlike action–outcome mappings, stimulus–outcome mappings depend on external, sensory signals as well as internal ones (concerning motivation), and they, too, can influence activity in accumulator networks.

Because these areas work together through their dense interconnections (Barbas 1988; Price & Drevets 2010), they permit mammals to choose either the action or the stimulus that predicts the best outcome, as updated in terms of current motivational value.

Table 4.1 Contribution of agranular PF areas to foraging choices

Region	Contribution
Medial agranular PF	Biases foraging among multiple choices of actions based on predicted costs/benefits
	Biases foraging toward outcome-directed choices for moderate-volatility environments
	Biases foraging toward habits for low-volatility environments
	Biases foraging toward extrinsic or intrinsic navigational rules
Orbital agranular PF	Biases foraging among multiple stimuli based on predicted sensory aspects of outcomes
	Biases foraging toward 'impulsive' foraging for exploiting available resources
	Biases foraging toward 'patient' foraging for exploring a distant resource

We think that this capacity provided an advantage over ancestral species, which lacked these cortical areas (Chapter 2). Because of their agranular PF cortex, mammals can switch foraging choices quickly in the face of changing circumstances. The previous chapter shows that they can learn a context in which habits should prevail or outcome-directed behaviours should, that they can learn when they should guide navigation by intrinsic or extrinsic rules, and that they can trade-off reward benefits with effort costs. This chapter shows that they can learn the contexts for 'impulsive' or 'patient' foraging.

In this sense, mammals can acquire contradictory behavioural knowledge that they can use to bias other behavioural control systems when circumstances change. Chapter 3 explains how this could work at the level of neural networks. Table 4.1 summarizes these ideas in relation to foraging choices. It is not meant to be exhaustive. For example, we neglect phenomena such as Pavlovian-to-instrumental transfer, the differential outcomes effect, and conditioned reinforcement. Lesions of the agranular OFC of rodents causes impairments on these tasks, as well as the ones that this chapter and Table 4.1 highlight.

Agranular areas in primates

Chapters 2 and 3 discuss the claim that the medial frontal cortex of rodents is either homologous or analogous to the mid-lateral PF cortex (area 46) in primates. No convincing evidence supports this suggestion and much opposes it. Here we deal briefly with a related contention regarding the orbital PF cortex.

Comparing agranular areas in rodents and primates

The orbital PF cortex in rats is entirely agranular, unlike the primate orbital PF cortex. Furthermore, it has connections that strongly resemble the agranular, but not granular, parts of the primate orbital PF cortex. It lies adjacent to allocortex, unlike granular PF cortex, and has a relatively direct influence over autonomic outputs, unlike granular PF cortex.

And yet, in spite of all of this evidence, some neuroscientists have suggested that the rat's agranular OFC corresponds to the entirety of the OFC in monkeys, including its granular areas (Uylings et al. 2003; Seamans et al. 2008; Schoenbaum et al. 2009). Chapter 2 explains

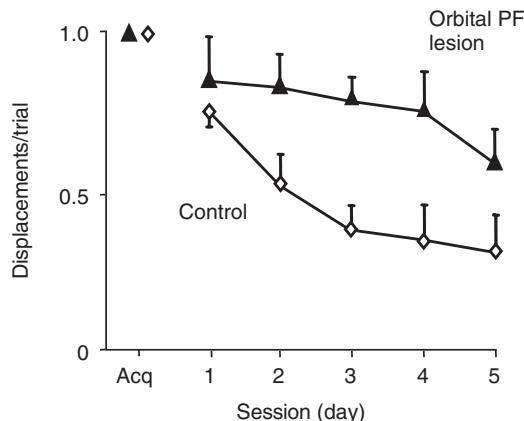


Fig. 4.4 Slowing of extinction learning by lesions of the granular OFC in monkeys. Monkeys first learn to displace an object in order to obtain a food reward. During this acquisition (acq) phase, the monkeys have 30 s to displace the object on each trial, and they do so on every trial. On subsequent testing sessions, called extinction trials, displacing the object can never produce food. Normal (control) monkeys decrease their displacements to less than half of trials over 5 days of testing. Monkeys with lesions of granular OFC displace objects at a higher rate than normal monkeys, although they significantly improve after 5 days of testing. Modified from Izquierdo A, Murray EA. Opposing effects of amygdala and orbital prefrontal cortex lesions on the extinction of instrumental responding in macaque monkeys. *European Journal of Neuroscience* 22:2341–6, © 2005, John Wiley and Sons, with permission.

that this idea takes one of two forms. One is that rats have a replica-in-miniature of the orbital PF cortex in monkeys; the other is that they have an amalgam of all of the areas that occur in monkeys. Both opinions depend on certain similarities between the orbital PF cortex in rats and monkeys, such as cell activity, neurochemical properties, connections, and lesion effects.

But the similarities invoked do not correspond to diagnostic traits, which is what one needs to establish homologies. As Chapters 2 and 3 argue, diagnostic traits distinguish areas from each other. Take, for example, the extinction of conditioned reflexes. Although rats with OFC lesions show slower than normal extinction (Kolb et al. 1974), lesions restricted to the granular OFC in monkeys have the same effect (Izquierdo & Murray 2005) (Figure 4.4), as do lesions that include the agranular OFC in monkeys (Büller 1969). Thus the similarity in question—that lesions of an area called orbital PF cortex cause a slowing of extinction learning—does not help us establish homologies.

Cell activity

Unfortunately, very little is known about the agranular parts of the OFC in primates, except for the anatomical knowledge that we reviewed earlier.

Rolls et al. (1994) recorded from cells in the orbital PF cortex that responded to salty, bitter, sour, and astringent tastes. From our inspection of their recording locations, they seem to have recorded mainly from the granular parts of areas 13 and 14, with additional

populations of cells in the agranular part of area 13 and in the agranular insular cortex. Cell in all of these areas responded to tastes.

In addition to gustatory inputs, visual and olfactory inputs help establish the identity of foods and fluids. In the study of Rolls and Baylis, cells in the orbital PF cortex responded both to conjunctions of vision and taste and to conjunctions of smell and taste. Most of the cells showing gustatory–visual or olfactory–visual conjunctions occurred caudally within the orbital PF cortex. Some were located in the agranular insular cortex and others in, or at least near, the agranular parts of area 13. The same properties occurred more rostrally in the orbital PF cortex, as well.

Rolls and his colleagues have also found that monkeys will press a lever to stimulate the granular part of area 13 through an electrode, an indication that they find the stimulation rewarding (Mora et al. 1980). Stimulation of area 11 does not have this effect. So cells situated more caudally in the OFC, including those responding to tastes or to conjunctions of sights or smells with tastes, seem to interact more directly with reward systems elsewhere in the brain than do the more rostral parts of the OFC.

Summary

Both rodents and primates have an agranular orbital PF cortex (see Figure 2.1), and we assume some conservation of its functions as inherited from their common ancestor. Unfortunately, we have little direct lesion or cell-recording evidence about the agranular orbital areas of monkeys, and so we acknowledge that this remains little more than an assumption. We do know, however, that the granular areas have dense interconnections with the agranular regions and that cells in the granular areas have sensory responses that we would expect on that basis, such as the conjunctions of sights, smells, and tastes that serve to identify particular foods and fluids. In the laboratory, of course, these foods and fluids serve as outcomes that guide behaviour.

Granular cortex

In contrast to the paucity of information on the agranular OFC in primates, its granular parts have been studied extensively. We discuss these findings in terms of the effects of lesions on associative mappings between stimuli and outcomes, the neural coding of these mappings in terms of particular outcomes and in terms of a ‘common currency’, the choice of rules based on outcomes, the updating of motivational valuations of these outcomes, and the accurate assignment of outcomes to choices.

Stimulus–outcome mappings

Monkeys, like other animals, use stimuli to predict outcomes and make foraging choices on that basis. Two kinds of experiments demonstrate these predictions: probabilistic-outcome experiments (Figure 4.5B) and deterministic-outcome experiments (Figure 4.5A). In the former, monkeys choose one of two or more stimuli that differ in the probability of yielding a reward; in the latter, monkeys learn to choose between two stimuli to always get a reward and change that choice when the reward contingency switches to the alternative choice.

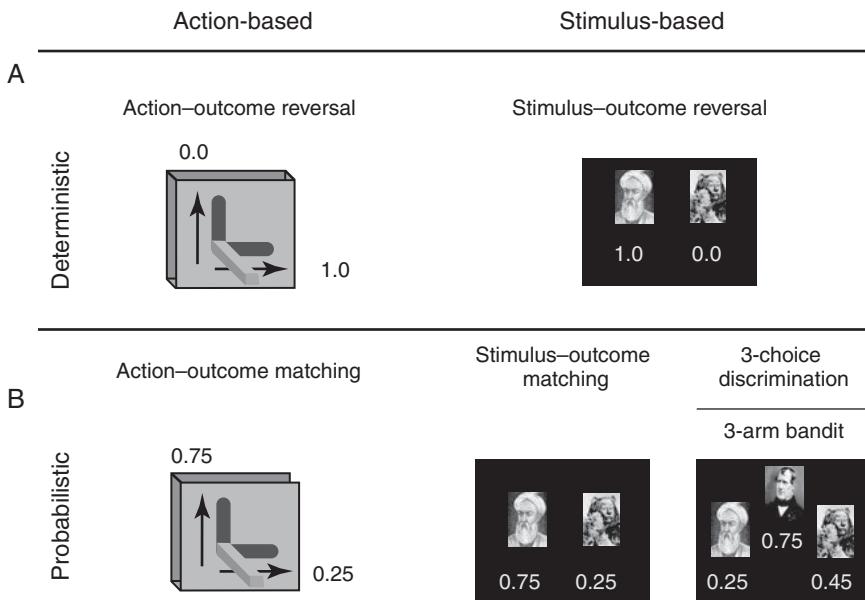


Fig. 4.5 Experiments that distinguish action-based (left) and stimulus-based (right) choices. (A) In deterministic action-based choices (left), moving a handle to the right is depicted as resulting in a reward every time, a proportion of 1.0, whereas moving the handle up never produces a reward (0.0). These outcomes later switch in the deterministic action reversal task. For stimulus-based choices (right), monkeys must contact one of the two pictures displayed on a touch-screen. The probability of reward for each choice was deterministic (0.0 or 1.0). (B) In probabilistic tasks, the likelihood of reward varies between 0 and 1, for choices between two actions (left) or two objects (middle). The numbers give the proportion of trials rewarded for each choice. These tasks are called matching tasks by reference to the ‘matching law’, not the matching-to-sample task. In the three-choice discrimination task (right), also called the three-arm bandit task, each of three choices pay off with a different probability, which varies over time. Modified from Rudebeck PH, Behrens TE, Kennerley SW, Baxter MG, Buckley MJ, Walton ME, Rushworth MF. Frontal cortex subregions play distinct roles in choices between actions and stimuli. *Journal of Neuroscience* 28:13775–85, © Society for Neuroscience, 2008, with permission.

Rudebeck et al. (2008) used the probabilistic method. In one version of the task, called stimulus–outcome matching (Figure 4.5B), they assigned four levels of probability, with two independent probability algorithms determining the level for each of two stimuli. Once the algorithm assigned a probability to a stimulus, that probability remained fixed over trials until the monkey chose that stimulus. The probabilities then changed, and so the animal had to repeatedly switch between the stimulus choices depending on their probability of payoff. In another probabilistic task, called the three-arm bandit task or the three-choice discrimination task, the monkeys learn to choose among three stimuli, each of which had probability of reward that varying as a function of trial number (Figure 4.5B).

Rudebeck et al. made lesions in the granular OFC in monkeys trained to perform the three-arm bandit task. These monkeys adjusted their choices to changing reward probabilities much more slowly than normal monkeys, which indicates an impairment

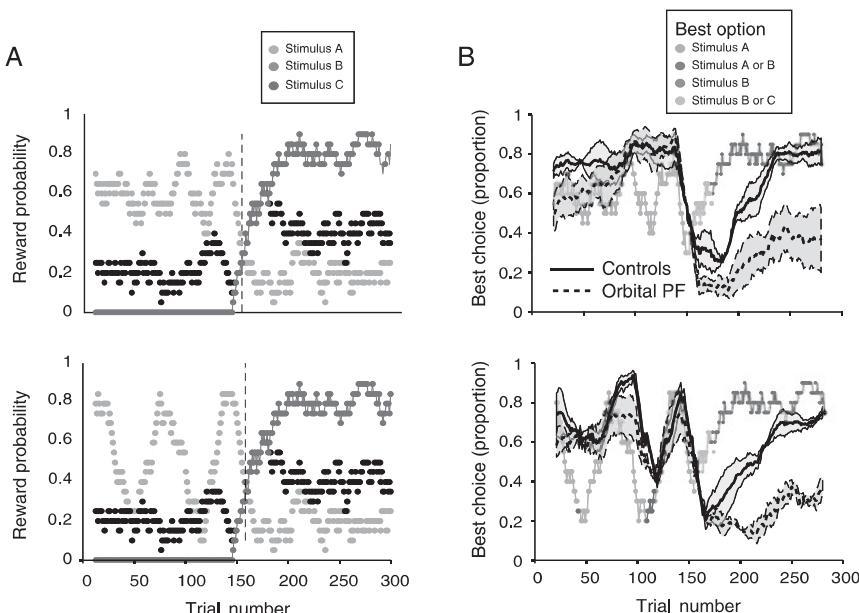


Fig. 4.6 Impairment in choice–outcome learning after granular OFC lesions in monkeys. (A) Probability of payoff for choosing each of three object-like stimuli, for the task illustrated in the lower right of Figure 4.5, the three-arm bandit task. The payoff rates vary as a function of trial number but do not depend on the monkey’s choices. (B) The proportion of trials that the monkey makes the best choice, as assessed in terms of payoff probability. The ordinate shows the proportion of choices of the highest value object (best choice) for normal (control) monkeys (solid line) and monkeys with lesions of the granular OFC (dashed line). Shading: SEM. The payoff probability of the best stimulus on any trial is plotted in grey. Top row: low volatility condition. Bottom row: high volatility condition. Reprinted from Walton ME, Behrens TEJ, Buckley MJ, Rudebeck PH, Rushworth MFS. Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. *Neuron* 65:927–39, © 2010, with permission from Elsevier.

in learning the associative mappings between stimuli and outcomes (Figure 4.6). Alternatively, we could describe the impairment in terms of learning (or updating) the associative mappings between choices and outcomes. In the remainder of this chapter, we use stimulus–outcome, object–outcome, and choice–outcome interchangeably.

The same monkeys, however, performed normally when they gained reward by choosing one of two actions rather than by choosing one of two stimuli. That task required the monkeys to choose either to lift or turn a lever to have some probability of obtaining a reward, which is the probabilistic version of the deterministic action reversal task that Chapter 3 describes.

In addition to monkeys with lesions of the granular OFC, Rudebeck et al. tested monkeys with lesions of cortex in the anterior cingulate sulcus on the stimulus–outcome matching task. They found no impairment in switching between stimuli after these medial PF cortex lesions, even though Kennerley et al. (2006) had shown that the same lesions impaired switching between actions.

Rudebeck et al. concluded that the medial PF cortex subserves the associative mappings between actions and outcomes, whereas the orbital PF cortex mediates the associative mappings between stimuli and outcomes. But Rudebeck et al. and Kennerley et al. reported results for lesions of cortex confined to the anterior cingulate *sulcus*. With larger lesions, especially those that include both the anterior cingulate sulcus and the anterior cingulate *gyrus*, a more mixed picture emerges. E. A. Murray et al. (personal communication) have reported that after these larger lesions monkeys have an impairment in a standard object reversal task. However, Meunier et al. (1997) directly compared the performance of monkeys with cingulate and orbital PF lesions, and the monkeys with orbital PF lesions made twice as many errors on the object reversal task.

The object reversal task thus continues to have a major influence on understanding the orbital PF cortex. Figure 4.5 A illustrates this deterministic task. When a reversal occurs, the reward contingency switches between two stimuli, typically without any additional cue other than reward or nonreward feedback.

In an early and influential study, Butter (1969) tested monkeys on three tasks: object reversal learning, spatial reversal learning, and extinction. In some monkeys, he removed the orbital PF cortex, together with the part of area 12/47 that lies on the orbital surface of the hemisphere. These monkeys had impairments on object reversal learning and extinction learning, but not on spatial reversal learning. In other monkeys, he removed the ventral PF cortex, including all of area 12/47. These monkeys had no impairment on the extinction task.

Many subsequent experiments have confirmed the functional distinction between orbital and ventral PF, as well as the deficit on object reversal and extinction learning after lesions of the orbital PF cortex (Dias et al. 1997; Izquierdo et al. 2004). For example, lesions of ventral PF cortex impair performance during the initial stages of object reversal learning, but orbital PF cortex lesions lead to a much more severe and long-lasting impairment (Rygula et al. 2010).

Butter concluded that lesions of the orbital PF cortex produced perseverative impairments in behaviour. And, since then, many studies of the orbital (or ventral) PF cortex have been interpreted in terms of perseveration, response inhibition, and behavioural inhibition (Roberts & Wallis 2000). According to this idea, lesioned monkeys have an impairment in inhibiting choices that have been rewarded previously, which produces perseveration.

Rudebeck and Murray (2008) re-examined this topic, and they did their analysis in several ways. First, in an analysis of the data illustrated in Figure 4.7, from Izquierdo et al. (2004), they counted the total number of errors until the monkeys had completed the switch from choosing the previously rewarded stimulus to choosing the currently rewarded one. As expected, Rudebeck and Murray found that monkeys with bilateral lesions of the orbital PF cortex reverse their choices between two objects more slowly than normal monkeys do. Furthermore, unlike normal monkeys, if tested on a series of reversals the lesioned monkeys fail to improve across this series of object reversal tests (Figure 4.7).

Next, Rudebeck and Murray analysed their results trial-by-trial, rather than averaged over blocks of trials as neuropsychologists have traditionally done. Kennerley et al. (2006)

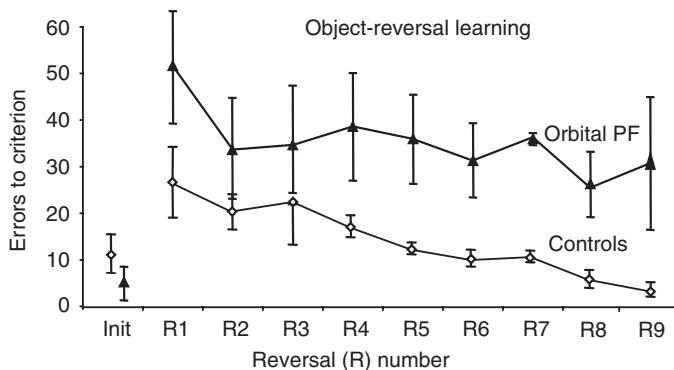


Fig. 4.7 Impairment in object reversal set in monkeys after lesions of the granular OFC. Number of errors to criterion performance on a two-choice, deterministic object discrimination task. In initial training (Init), with no reversals, monkeys learn to discriminate between two objects with relatively few errors. The orbital PF cortex plays no role in this kind of learning because monkeys only need to learn which objects are positive in value and which are neutral. Once the simple classification of an object as positive or neutral no longer solves the problem, the orbital PF cortex becomes necessary. R1 . . . R9 indicate nine serial reversals, in which over time both objects become positive and neutral in alternating blocks of trials. Monkeys with lesions of the granular OFC learn these reversals more slowly than normal (control) monkeys, and they fail to improve consistently over the nine reversals. Error bars: SEM. Reproduced from Izquierdo A, Suda RK, Murray EA. Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. *Journal of Neuroscience* 24:7540–8, © Society for Neuroscience, 2004, with permission.

had used the same kind of analysis for their action-reversal experiment on the medial PF cortex (Chapter 3). Rudebeck and Murray measured the number of errors made in two ways, both of which occurred after the stimulus–outcome mappings had reversed.

First, as illustrated in Figure 4.8A, Rudebeck and Murray counted the number of errors made prior to the first correct choice and compared these data to the number of errors made after the first correct choice. The largest difference between normal and lesioned monkeys occurred after the first correct choice.

Second, as illustrated in Figure 4.8B, the authors examined how likely animals were to persist with a correct response as a function of recent rewards, which served as positive feedback. To do this, Rudebeck and Murray compared performance one trial after an error, one trial after an error-correct sequence, one trial after an error-correct-correct sequence, etc. Figure 4.8B shows that lesions of the orbital PF cortex lead to an inefficiency in using positive feedback. Even when two, three, or four correct (and rewarded) responses followed an error, monkeys with orbital PF cortex lesions made many more errors than did normal monkeys. They performed almost normally, however, in response to the negative feedback that comes from an unrewarded choice (Rudebeck & Murray 2008). Clarke et al. (2008) found a similar result in marmosets.

Taken together with the similar analysis by Kennerley et al. (2006) for action–outcome learning, the results of Rudebeck and Murray provide further support for the dissociation

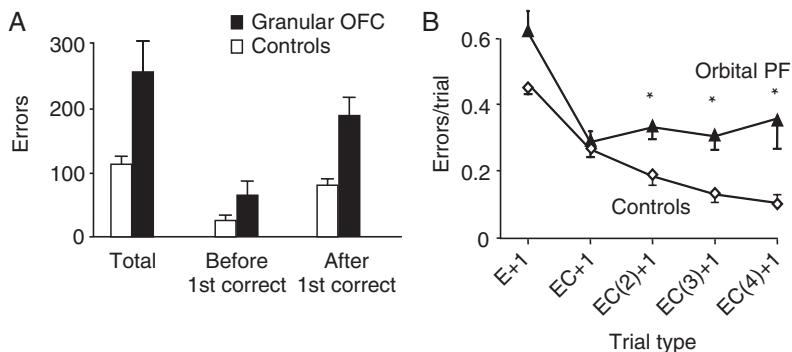


Fig. 4.8 (A) Errors made on the object reversal task, before and after the first correct choice. For monkeys with lesions of the granular OFC (black bars) and for normal (control) monkeys (white bars). Most errors came after the first correct choice. (B) Trial-by-trial performance after an error (E + 1), after a sequence of an error followed by one correct choice (EC + 1), after an error followed by two successive correct choices [EC(2) + 1], etc. Monkeys with lesions of the granular OFC (filled triangles) fail to benefit as efficiently as normal (control) monkeys (white diamonds) from the positive feedback that comes from rewards. Asterisk: statistically significant difference. Error bars: SEM. Reproduced from Rudebeck PH, Murray EA. Amygdala and orbitofrontal cortex lesions differentially influence choices during object reversal learning. *Journal of Neuroscience* 28:8338–43, © Society for Neuroscience, 2008, with permission.

of function between the medial PF cortex and the orbital PF cortex. In the family of tasks illustrated in Figure 4.5, lesions of the orbital PF cortex cause impairments in learning about altered stimulus–outcome associations but not about altered action–outcome associations. By contrast, lesions in the medial PF cortex—and more specifically those in the anterior cingulate cortex—cause impairments in learning about altered action–outcome mappings with have smaller and less reliable effects on learning stimulus–outcome mappings.

A recent lesion study in humans has produced a similar conclusion. Camille et al. (2011) studied patients with lesions of the dorsal anterior cingulate cortex or the orbital PF cortex. For the latter, the maximal area of overlap was found in the granular OFC, near its boundary with the agranular OFC. But in most patients the lesions involved both regions. Camille et al. used the same kind of analysis as in the monkey experiments and found similar results. In the stimulus–outcome task, subjects chose between a coloured deck of playing cards that either yielded either the gain or loss \$50 of play money. A deck of one colour yielded a gain on 86% of trials, the other produced a gain on 14% of the trials. In the action–outcome task, subjects chose between pronation and supination movements of the forearm with the same outcome contingencies. After the subjects learned the correct choice, the contingencies reversed, as in the monkey experiments with action reversals and object reversals.

Camille et al. measured the proportion of trials in which subjects erroneously shifted their choice after positive feedback. Such shifts were errors because the feedback indicated that they should persist with their previous choice. Orbital PF cortex lesions caused

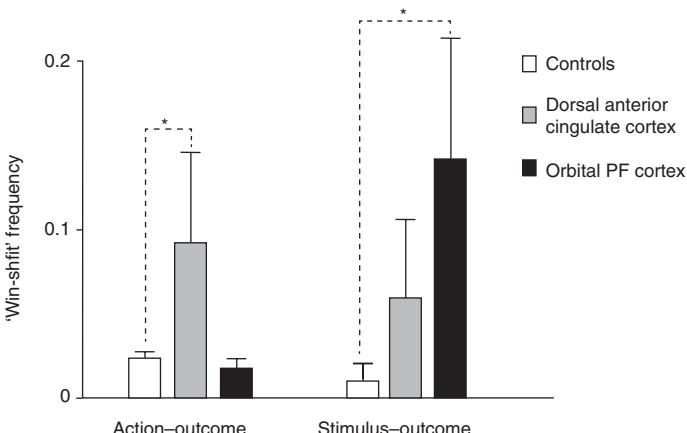


Fig. 4.9 Reversal impairments in patients with lesions of the orbital PF cortex (black bars) and the anterior cingulate cortex (grey bars), compared with control subjects (white bars). For the object reversal task, subjects chose between differently coloured decks of cards; for the action reversal task, they chose between pronation or supination movements. Shifting after a 'win', the 'win-shift' frequency, is the same kind of error as illustrated for monkeys in Figure 4.8. Error bars: SEM. Asterisks: statistically significant contrasts. Reproduced from Camille N, Tsuchida A, Fellows LK. Double dissociation of stimulus-value and action-value learning in humans with orbitofrontal or anterior cingulate cortex damage. *Journal of Neuroscience* 31:15048–52, © Society for Neuroscience, 2011, with permission.

an impairment in the stimulus–outcome reversals, but these patients behaved like control subjects on the action–outcome task (Figure 4.9). Anterior cingulate cortex lesions, by contrast, caused an impairment in the action–outcome reversals compared to control subjects. Patients with these lesions also made more errors on the stimulus–outcome task than did control subjects, but this difference did not reach statistical significance (Figure 4.9).

In addition to demonstrating a dissociation of function between orbital and medial PF cortex, the findings of Rudebeck and Murray in monkeys and of Camille et al. in humans demonstrate that subjects with orbital PF cortex lesions use positive feedback inefficiently but use negative feedback nearly normally. These findings directly contradict the idea that subjects with OFC lesions perseverate because of an inability to inhibit learned responses. Indeed, the subjects in these experiments switch from their previous choice nearly normally, based on negative (error) feedback. Instead of perseveration, the impairment can instead be characterized as one of insufficient persistence: the opposite of perseveration. Chapter 10 takes up behavioural inhibition and perseveration in more detail and for the PF cortex as a whole.

In object reversal experiments, the monkey receives two kinds of feedback indicating that a stimulus–outcome mapping has changed: an expected reward fails to occur or an unexpected reward occurs. Both cases result in a 'reward-prediction error' (Schultz & Dickinson 2000). Studies of dopaminergic neurons in the midbrain show an increase in activity when an unexpected reward arrives and a decrease when an expected reward fails

to materialize (Schultz 1998). In Chapter 3, we refer to this property as a signed error signal, in order to contrast it with the unsigned error signals that occur in the medial PF cortex. The dopaminergic cells send their axons to the striatum and to the cortex, among other brain structures, which use these signed error signals to adjust behaviour.

O'Doherty et al. (2003) used a temporal-difference model of learning, which depends on the reward-prediction error. They scanned human subjects as they performed a task that used complex patterns of colours and shapes as stimuli. One of these stimuli signalled the delivery of a drop of sweet fluid, a second stimulus signalled no fluid, and a third signalled a neutral-tasting fluid. However, on some trials the predicted event failed to occur. O'Doherty et al. looked for activations matching the pattern expected for signed reward-prediction error signals: activations that decreased when the sweet taste failed to occur as expected and increased when it occurred unexpectedly. The orbital PF cortex and a ventral part of the striatum had activations that matched this pattern.

Of course, these signals can also be found in other parts of the PF cortex. As Chapter 3 mentions, neurons in the medial PF cortex of monkeys also encode reward-prediction errors of various kinds (Matsumoto et al. 2007; Seo & Lee 2007; Hayden et al. 2011a). However, for the medial PF cortex the error signals seem to mainly involve the choice among actions, whereas in the imaging study by O'Doherty et al. (2003) they involved the choice among stimuli.

Coding stimulus–outcome mappings

Chapter 3 explains that cells in the medial PF cortex have activity that reflects the value of visual stimuli, in terms of both costs and benefits. As we mentioned there, similar activity occurs in the orbital PF cortex. Kennerley et al. (2009), for example, studied variables such as the amount of reward, the probability of reward, and the effort cost of multiple key presses. Cells in the orbital PF cortex encode these variables both when monkeys have to choose between stimuli of different value (Seo & Lee 2008) and when they simply observe the association between stimuli and value, as occurs in Pavlovian conditioning (Morrison & Salzman 2009).

In a nutshell, the literature shows that neuronal activity in the orbital PF cortex encodes not only the value of objects and rewards (Padoa-Schioppa & Assad 2006) and the probability of obtaining reward (Kennerley et al. 2009), but also many other factors that contribute to foraging choices. These factors encompass both beneficial and detrimental outcomes (Morrison & Salzman 2009), including costs in terms of effort (Kennerley et al. 2009), time (Roesch & Olson 2005), and risk (O'Neill & Schultz 2010), as well as outcomes that would have followed rejected choices (Abe & Lee 2011) and confidence in the success of a choice (Kepcs et al. 2008).

Related neurophysiological studies have stressed relative value, as reflected in preferences among different kinds of foods and fluids. Tremblay and Schultz (1999) studied neuronal activity in the granular OFC. A cell might, for example, have greater activity in response to an apple when monkeys choose between an apple and cereal but less activity in response to an apple when monkeys choose between bananas and apples. These cells encode the relative value of foods. In addition to relative valuations, some neurons in the

granular orbital PF cortex encode value independent of the choices that are available (Padoa-Schioppa 2009).

These properties follow from connections, but it may seem puzzling that cells in the medial PF cortex also encode the value of outcomes predicted by stimuli (Kennerley et al. 2009). Activations also occur in medial PF cortex for choices among objects (Behrens et al. 2007; Glascher et al. 2009), and there might be some effects of lesions there on the choices among objects (Camille et al. 2011). A strict dichotomy between action–outcome and stimulus–outcome coding might, at first glance, seem to preclude these results. As discussed earlier, lesions of the orbital PF cortex lead to impairments on reversals between objects (Rudebeck et al. 2006b) and lesions of the medial PF cortex lead to impairments on reversals between actions (Kennerley et al. 2006).

One might suppose, based on these results, that the medial PF cortex should lack activity that reflects stimulus–outcome conjunctions. Chapter 1, however, explains why lesion studies can yield results that seem inconsistent with either recording or imaging results, at least on the surface. Part of the reason arises from the fact that the orbital and medial PF cortex work together. Through dense interconnections, they can combine stimulus–outcome conjunctions with action–outcome conjunctions.

The concept of affordances helps explain these high-order representations. The term affordance refers to the actions that are associated with an object or class of objects. By combining object–outcome and action–outcome associations, the medial PF cortex might encode the outcome associated with acting on an object in a certain way, as occurs during object manipulation. These representations thus include an object’s features and the actions that are associated with the object. This idea could explain why object–value conjunctions occur so prominently in the medial PF cortex; objects can be involved in many different kinds of action. These cells might also encode something more abstract than concrete action–outcome associations, such as the outcome predicted for making any action at all with an object or for making some class of actions with it.

If some parts of the medial PF cortex represent conjunctions of actions, objects, and outcomes, this might account for the imaging and cell-recording results, as well as the inconsistent effects of medial PF lesions on choices between objects. For example, we mention earlier some unpublished evidence that large anterior cingulate lesions impair object reversal learning (E. A. Murray, personal communication), although in similar tasks monkeys perform normally after smaller lesions (Rudebeck et al. 2006b).

A strict dichotomy between medial and orbital PF cortex function also seems inconsistent with another result. Just as cells in the medial PF cortex reflect stimulus–outcome associations (Kennerley et al. 2009), cells in the orbital PF cortex reflect action–outcome associations. Tsujimoto et al. (2009) showed that cells in the granular OFC encode a monkey’s choice of action, but only around the time that feedback (reward or no reward) occurs. These findings do not disagree with those from lesions. The monkeys in the experiment of Tsujimoto et al. chose between two visible objects (white squares) that remained visible on a video monitor throughout each trial. One could argue, therefore,

that the cells encoded a choice between objects around the time of feedback, a finding we take up again later.

One of our core principles is that the connections of the orbital PF cortex explain why it alone can perform its functions. The orbital PF cortex, but not the medial PF cortex, receives inputs from the inferior temporal cortex, which represents the colour, shape, and visual texture of objects. And the orbital PF cortex, but not the medial PF cortex, receives direct inputs from gustatory, visceral, and olfactory areas of cortex, all of which relate to specific outcomes. So it is easy to see why the orbital PF cortex represents stimulus–outcome conjunctions and why it plays a necessary role in choosing objects based on outcomes.

Valuation in a common currency

Animals must be able to compare the value of different resources because foraging choices often involve trade-offs. An animal may be both thirsty and hungry, for example. How much of a particular fluid is motivationally equivalent to a given amount of a food? One possibility is that animals represent the value of everything in a ‘common currency’ in order to make such choices. The idea is that the different potential outcomes of choices, such as sex, warmth, and food, are represented in a single dimension so as to guide choices (Montague & Berns 2002). The reward-prediction error signal has this property.

If a ‘common currency’ exists in neural representations, then we should see a similar magnitude of activity in response to different types of equally preferred rewards, irrespective of the nature of the reward. Padoa-Schioppa and Assad (2006) found neurons in the orbital PF cortex of monkeys that encoded the value of the juice, irrespective of the kind of juice. In this sense, some orbital PF cortex cells code for the abstract value of reward: reward in a common currency.

For human subjects, money serves as a reward, and it is abstract in that it can be exchanged for a variety of goods. O’Doherty et al. (2001) taught human subjects a visual discrimination task for monetary reward, and the activation for gains versus losses lay in the rostral ventromedial PF cortex, area 14. Kim et al. (2011) scanned subjects while they saw visual stimuli, some of which were associated with different amounts of money and others of which were associated with different amounts of juice. There was activation in the ventromedial PF cortex (area 14) related both to the amount of money and to the amount of juice.

Likewise, Sescousse et al. (2010) compared activations for money to those for erotic stimuli, arguing that the latter corresponded to a primary reward. They found a rostro-caudal organization with primary reward leading to activation caudally and more abstract, ‘common-currency’ rewards leading to activations rostrally. Others have made similar suggestions (Kringelbach & Rolls 2004).

Clearly, the ability to compute valuations in a common currency has advantages. Animals often enough have to balance a variety of costs and benefits. And, at a certain level, a system that deals entirely with a single dimension of foraging outcomes can function effectively. Augmenting this system with high-dimensional information about

specific outcomes also provides advantages, especially for learning about the contrasts among outcomes. Later we discuss evidence that lateral parts of the OFC encode outcomes in a high-dimensional way, whereas medial parts encode outcome in a single ‘common currency’ dimension.

In addition to positive valuations, the granular OFC also plays a role in negative ones. In a study of snake fear, for example, macaque monkeys reached over either a neutral object or a rubber snake to retrieve food. Normal monkeys reached over the snake only after a long delay, and sometimes refused to do so at all. After lesions of the granular OFC, however, monkeys reached for the food quickly and did so similarly for neutral objects and snakes (Izquierdo et al. 2005). One interpretation of this result is that the monkeys did not encode the negative valuation of the snake.

Visual rules based on outcomes

In the examples given so far, the associated outcomes involved representations of objects, whether food, juice, or money. But one can also associate outcomes with more abstract representations, such as those for rules. And the tests used to discern these mappings are similar, as well. Just as experiments can assess the ability of monkeys to switch between the choice between objects, so one can assess the ability to switch between rules.

Buckley et al. (2009) studied monkeys that had learned a matching-to-sample task involving two different kinds of matching rules. After the sample stimulus had appeared and a delay elapsed, the monkeys faced three choice stimuli. One of the potential choices matched the shape of the sample, another matched its colour, and the third matched neither shape nor colour. The monkey had to use one of two matching rules: matching for shape or matching for colour. First, they learned one rule to a high level of performance, and then the experimenters changed the rule. In the subsequent series of trials the monkeys had to use the newly established rule with no cue other than reward or nonreward to guide them. These experiments resemble the object reversal and action reversal tasks described earlier.

To study the effect of orbital PF cortex lesions, Buckley et al. employed the same trial-by-trial analysis as Rudebeck and Murray (2008) used, which an earlier part of this chapter explains. This analysis measures how likely animals were to persist with a correct rule as a function of recent rewards. After a rule change, Buckley et al. compared performance one trial after an error, one trial after an error-correct sequence, and so forth. Before the lesion, the monkeys performed at 77% correct after an error-correct sequence. That is, they used the positive feedback on the correct trial to improve their performance the next time they had to choose between the two visual rules. After orbital PF cortex lesions, the monkeys performed at only 50% correct after an error-correct sequence. This finding shows the orbital PF cortex plays an important role in associating outcomes with a choice among rules as well as a choice among objects.

Updating motivational valuations

The current value of a specific food reward also reflects the current biological needs or state of an animal. Chapter 3 explains that the devaluation task manipulates the value of

a food, sometimes by a selective satiation procedure: monkeys consume one kind of food to satiety before a testing session.

Izquierdo et al. (2004) taught monkeys that the choice of one set of objects produced one kind of food, and the choice of another set of objects produced another kind of food. In all of the training sessions, an object associated with one of the two foods (a positive object) was paired with an object that, if chosen, led to no reward (a neutral object). The monkeys learned these object–outcome mappings very well. The monkeys then consumed one of the foods to satiety, a procedure that devalues the food. Then, in a subsequent test session, while the monkeys were satiated, they faced a choice between two positive objects, one for each kind of food. Without any experience in choosing between the two positive objects, normal monkeys nevertheless tended to avoid choosing objects that were associated with the devalued food. Instead, they chose objects associated with the outcome that best suited their current motivational state: the more highly valued food. They saw each pair of objects only once and so could not base their choices on experience during the testing session. Therefore the monkeys must have made their choice based on a prediction about the outcome, with the value of that outcome updated in terms of their current motivational state.

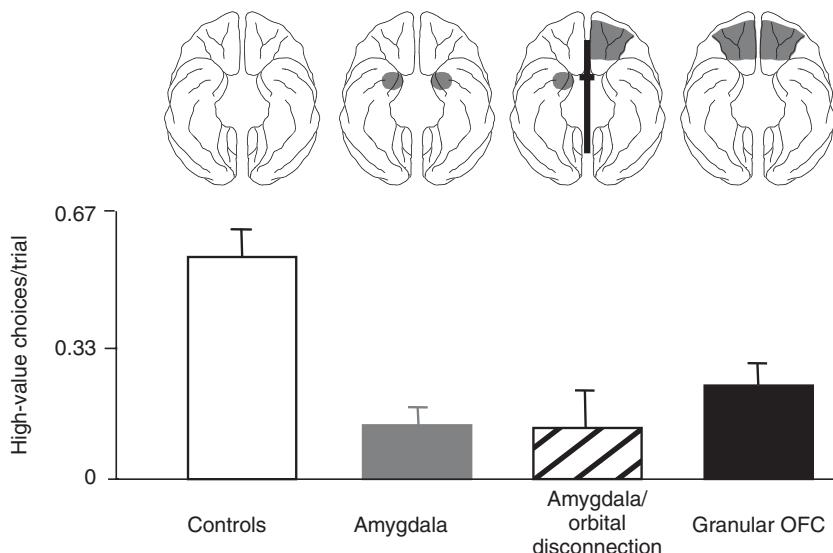


Fig. 4.10 Effect of various lesions on choices on performance of the devaluation task. The drawings at the top depict the three lesions on a ventral view of a macaque monkey brain. Shading indicates approximate location of selective amygdala lesions (beneath the brain surface) or of the granular OFC. The heavy black lines between the hemispheres indicate transection of the corpus callosum and the anterior commissure. Ordinate: the proportion of high value choices per trial, that is, choice of the object that had not been devalued by prior selective satiation. Error bars: SEM. Modified from Murray EA, Izquierdo A. Orbitofrontal cortex and amygdala contributions to affect and action in primates. *Annals of the New York Academy of Sciences* 1121:273–96, © 2007, John Wiley and Sons, with permission.

By contrast, monkeys with lesions of the granular OFC did not avoid the devalued choice nearly as effectively as normal monkeys (Figure 4.10). Instead, they tended to choose objects based on their original food preferences. So if a lesioned monkey originally preferred one kind of food, they tended to choose the objects associated with that food even though they had just consumed it to satiety.

As Figure 4.10 illustrates, a similar effect follows a bilateral lesion of the amygdala, and it also follows a unilateral lesion of the amygdala combined with a lesion of the granular orbital PF cortex on the other side of the brain (Baxter et al. 2000). Lesions of the ventral PF cortex or the mid-lateral PF cortex do not have this effect (Baxter et al. 2009).

Other evidence indicates that the updating of motivational valuations occurs automatically, as monkeys consume a food to satiety. Inactivation of the amygdala during the feeding causes the impairment, but later inactivation does not (Wellman et al. 2005). This finding shows that interactions between the amygdala and the orbital PF cortex must occur during feeding, as the food's value changes due to satiation.

The connections of the orbital PF cortex explain why it plays a crucial role in this function. To make the best foraging choice, monkeys must make this choice based on current motivational valuations, and this requires its connections with the amygdala. Monkeys with lesions of the granular OFC or the amygdala remain hungry and therefore motivated to forage for food, but they no longer make their choices in accord with current needs.

The lesion experiments on monkeys implicate the granular OFC in updating valuations. Imaging results in people point to the same conclusion. Gottfried et al. (2003) taught human subjects to associate one visual stimulus with a certain odour and to associate a different visual stimulus with another odour. The subjects then consumed to satiety a food with one or the other odour and later showed the devaluation effect in a preference test, much like the monkeys. Changes in activation in the amygdala and the orbital PF cortex paralleled the change in preference. The peak activation coordinate occurred in the granular OFC. Of course, this finding does not rule out a role for the agranular OFC in other kinds of valuation updating.

Likewise, Critchley and Rolls (1996) recorded from cells in the granular OFC while monkeys smelled odours or saw visual stimuli that were associated with specific juices, such as blackberry juice. After the monkeys consumed one type of juice to satiation, cells decreased their response to the olfactory or visual stimulus that was associated with that kind of juice.

Putting what we say here together with Chapter 3, we can see that the updating of motivational valuations occurs for both the medial and orbital PF cortex, for both action–outcome and stimulus–outcome conjunctions, for both ‘internally’ guided and externally guided choices, and for both agranular and granular PF cortex. Some combinations have yet to be tested, such as the specific contribution of the agranular OFC in monkeys. But we assume that value updating occurs through the interaction of the amygdala with all of the cortical areas connected to it. We do not mean to imply that this kind of updating encompasses all of the amygdala’s functions, but it seems to be an important one.

Credit assignment

In the object-reversal experiments described earlier, the outcome depended on the monkey's choice between two objects. A crucial aspect of foraging involves learning what choices cause a behavioural outcome, and this knowledge is rarely certain. Walton et al. (2010) therefore devised an experiment that explored how the orbital PF cortex assigns causal responsibility for a particular outcome to a particular choice among stimuli.

On each trial of the three-arm bandit task (Figure 4.5B), the monkeys saw three stimuli, which consisted of several shapes and colours. Each stimulus had a different probability of producing a reward if chosen. These probabilities changed over time, in both a high-volatility and low-volatility mode. Figure 4.6 shows the reward probability for the three stimuli as a function of time. Faced with this problem, monkeys will most often choose the stimulus that produces the largest payoff. In the experiment illustrated in Figure 4.6, after about 145 trials the stimulus that had not previously paid off at all began to do so. After a number of trials, its likelihood of paying off exceeded the other two possible choices. Normal monkeys take some time to discover this fact, but after ~150 trials they consistently choose this newly optimal stimulus. It is worth emphasizing that unlike some similar experiments, in this one the monkeys' previous choices did not affect the payoff probability: the outcomes varied according to a predetermined schedule.

Monkeys with lesions of the granular OFC took much longer to discover the new highest-value stimulus after its probability of payoff exceeds that of the competing stimuli. Figure 4.6 shows that, after about 10 trials, the choices of the normal monkeys and the monkeys with orbital PF cortex lesions diverged, and that thereafter the lesioned monkeys made decidedly suboptimal choices that persisted for more than 150 trials, with only a little improvement.

In principle, the impairment might reflect a loss of behavioural flexibility, but the high-volatility condition ruled out this explanation. As Figure 4.6 shows, when two of the probabilities fluctuated markedly both normal and lesioned monkeys flexibly changed their choices, although not quite to the same degree. If the monkeys lacked flexibility or were perseverating, they should have stuck with the same choice.

Walton et al. then made a key breakthrough. They carefully analysed the results for trials after the formerly low-value stimulus exceeded the others. At that point, it became the 'newly best' stimulus, in contrast to the 'previously best' stimulus. If, after its big increase in value, the monkey selected this 'newly best' stimulus and received a reward, it should be more likely to choose the same stimulus again on the next trial. Normal monkeys did exactly that, but monkeys with granular OFC lesions did not.

Figure 4.11 shows what the monkey did and why. Positive values on the y-axis show the degree to which the monkeys increased their choice of the 'previously best' stimulus. Negative values indicate how much they shifted their choice to the 'newly best' stimulus. This plot illustrates the key finding. For normal monkeys, receiving a reward for choosing the 'newly best' stimulus led a shift of their choices to that stimulus. For lesioned

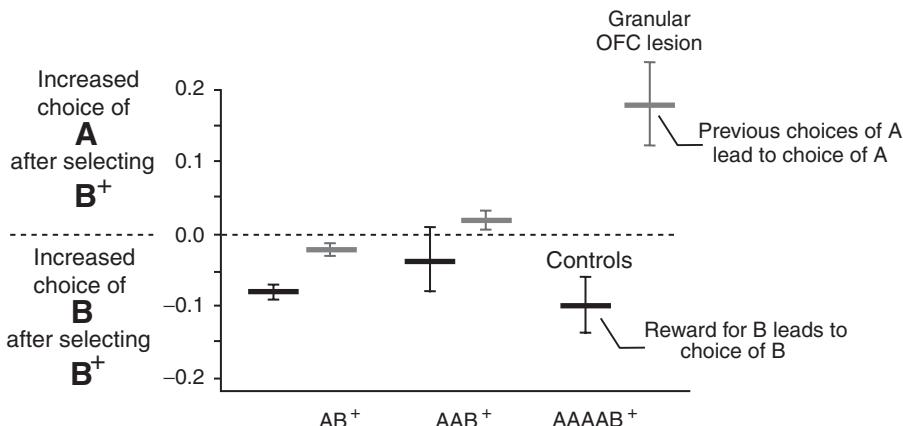


Fig. 4.11 Credit assignment based on a single event. The plot shows the mean (horizontal lines) and SEM for normal (control) monkeys (black) and monkeys with lesions of the granular OFC (grey). The abscissa divides trials according how many trials with stimulus A preceded a trial on which choosing stimulus B led to a reward (+). Ordinate: positive values indicate the increased likelihood of choosing stimulus A after being rewarded for choosing stimulus B; negative values indicated the increased likelihood of choosing stimulus B in that circumstance. Adapted from Walton ME, Behrens TEJ, Buckley MJ, Rudebeck PH, Rushworth MFS. Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. *Neuron* 65:927–39, © 2010, with permission from Elsevier.

monkeys, the opposite occurred. And the longer the history of choosing the ‘previously best’ over the ‘newly best’ stimulus, the more often they chose the wrong stimulus.

These results suggest that the normal monkeys recognized the causal link between their choice of the ‘newly best’ stimulus and the outcome, but the lesioned monkeys did so much less accurately. The lesioned monkeys, instead, made their choices based on a longer history of having chosen the ‘previously best’ stimulus. They appear to mistakenly assign the reward that they obtained for choosing the ‘newly best’ stimulus to some average of their prior choices of the ‘previously best’ stimulus, with more weight placed on more recent choices.

Figure 4.12 explains the basis for this conclusion graphically, in matrix form. The figure shows the strength of the mapping between the outcome and the object chosen on a trial. The ‘proper’ assignment would map the outcome that occurred n trials back from the current trial to the choice that the monkey had made on that trial. That is, they should attribute the outcome from the previous trial to their choice on that trial (one back), and they should attribute the outcome three trials earlier to the choice they had made three trials earlier (three back). Normal monkeys establish strong associative mappings for the ‘proper’ assignment, in this sense. Only weak mappings, if any, go from the outcome to an ‘improper’ choice. The figure shows some examples, such as a weak mapping between the outcome three trials back with the choice made one trial back. Monkeys with lesions of the granular OFC cannot establish the strong, ‘proper’ mappings as effectively as normal monkeys.

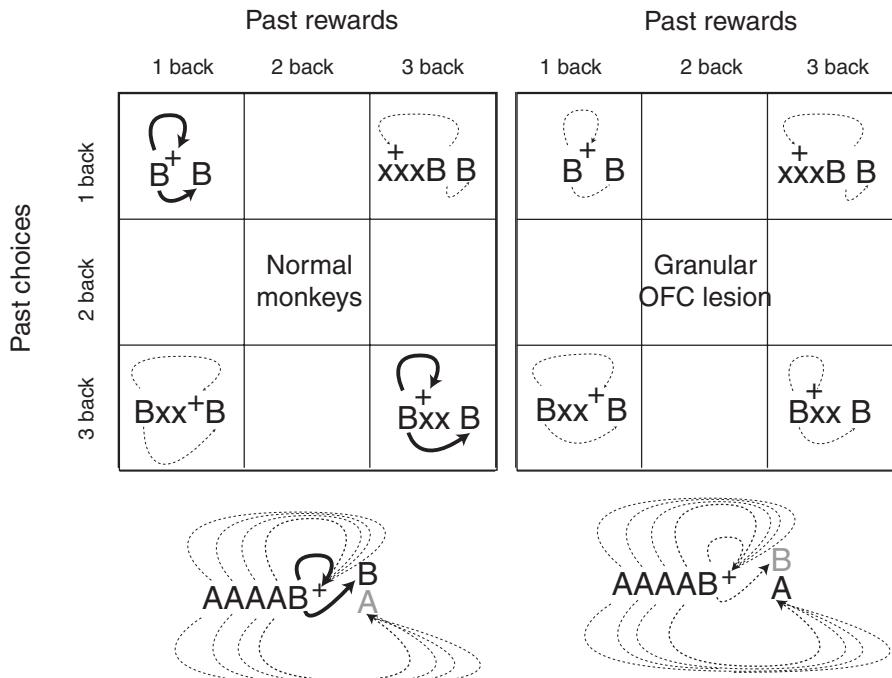


Fig. 4.12 Each matrix shows selected mappings between choices and rewards. The monkeys chose among three stimuli, A, B, and C. B is the rewarded choice, as indicated by the plus sign (+). x indicates an alternative choice (A or C). Left: credit assignment in normal (control) monkeys, based on a single event. For example, in the upper left and lower right cells of the matrix, the choice of stimulus B is assigned to the outcome (+) on the appropriate trial, which promotes the choice of B in the future. Alternatively, one could say that the outcome is assigned to the choice. Solid lines indicate strong influences; dashed lines indicate weak ones. Right: impairment in assigning single choices to the outcomes in monkeys with lesions of the granular OFC. Only the weak influences remain. Beneath each matrix is summary depiction of this mechanism. Black indicates a chosen stimulus; grey, a stimulus not chosen. Strong influences reflect single choice-outcome events (solid lines), and weak ones reflect a time-weighted average over many outcome events, as denoted by different shades of grey (dotted lines). As a result of losing the strong influence of a single feedback event, lesioned monkeys more often choose stimulus A (right), whereas on the basis of proper credit assignment, normal monkeys more often choose stimulus B (left), as shown in Figure 4.11.

The findings of Walton et al. can thus be understood as showing that the granular OFC improves ‘credit assignment’, defined as the assignment of an outcome to the choice that seemed to cause it. One could restate this as the assignment of a choice to the outcome it seemed to cause: a choice–outcome mapping. Thus, the function of the granular OFC seems to involve a significant improvement in using single outcome events to assign causal responsibility to single choice events.

Crucially, monkeys with lesions of the granular orbital PF behave something like rats. Like rats, these monkeys have an agranular OFC, and like rats they base their choices on an approximation of the choice–outcome mappings by associating the overall history of

choices and outcomes, with a recency bias sometimes called melioration (Herrnstein & Prelec 1991). Melioration refers to the process of increasing responses that have been effective recently, averaged over time, without reference to specific events. So like rats, which lack a granular OFC for a different reason, monkeys with lesions of the granular OFC no longer make foraging choices based on the ‘proper’ assignments of choice events to outcome events, and instead make them based on broader averages, with a bias toward recent successful choices.

Tsujimoto et al. (2009) showed how credit assignment could work at the single-cell level in a neurophysiological experiment mentioned earlier. They studied neuronal activity during a cued-strategy task. A visual cue instructed monkeys to either stay with or shift from their previous choice between two spatial goals. They found that neurons in the granular OFC encoded the monkey’s choice of a spatial goal when the outcome occurs. The representation of choices around the time of the outcome could promote accurate credit assignment.

Tsujimoto et al. also compared the encoding of these choices on correctly and incorrectly performed trials, as Chapter 3 mentions for the polar PF cortex. They assumed that on correct trials the monkeys based their choice on a particular cognitive process: a cued stay–shift strategy. The monkeys performed the task very well, so ‘lucky’ guesses could not contribute much to the result. The monkeys did make a few errors, which probably resulted from a random goal choice after they had forgotten something important to the task. Unlike cells in other parts of the PF cortex, such as the polar and mid-lateral PF areas, cells in the orbital PF cortex had the same activity on correct and error trials (Figure 4.13). This finding indicates that the orbital PF cortex encodes choices regardless of the cognitive process that generates them, at least on a task that has fixed reward probabilities and does not require learning (Tsujimoto et al. 2011b). In such circumstances, if the orbital PF cortex assigns credit to a particular choice, it seems to do so regardless of how the monkeys made that choice.

Subdivisions of granular OFC

Up to this point in this section, we have discussed the granular OFC as a whole. Yet in the beginning of this chapter, we quoted various anatomical authorities who divided this region into at least three cortical fields: areas 11, 13, and 14. Based on connections, Carmichael and Price placed area 14 within a group of areas they call the medial network, to which they attribute visceromotor functions. By contrast, area 11 and most of area 13 fall within an orbital network, which has strong connections with sensory areas of cortex, such as the inferior temporal cortex.

Recent experiments have explored the specializations of function for medial parts of the granular OFC, as opposed to lateral parts. One set of these studies has focused on associational mappings, the other on motivational valuations. For convenience, we use the terms lateral and medial OFC, but readers should keep in mind the fact that we refer in all cases to the granular OFC.

Noonan et al. (2010) specifically compared the role of the medial and lateral parts of the OFC, using the three-arm bandit task explained earlier (Figure 4.5B). Medial lesions,

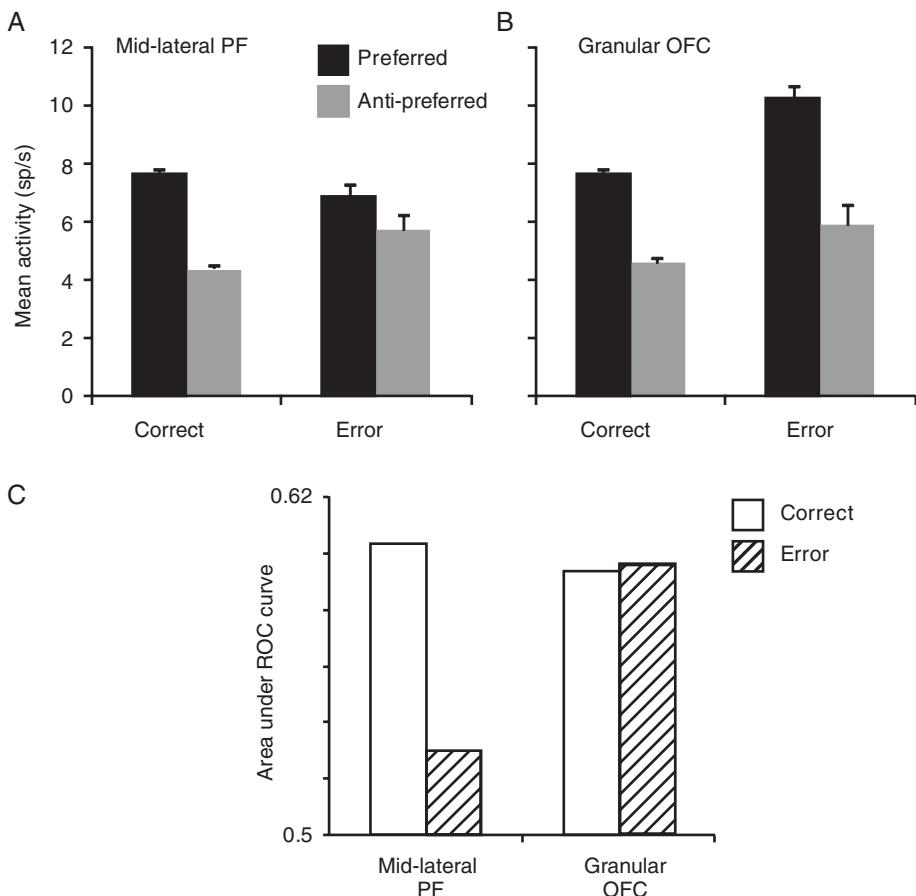


Fig. 4.13 Cell activity encoding choices during the feedback period in monkeys. (A) For the mid-lateral PF cortex, the mean population activity for the preferred (black) choice significantly exceeds that for the anti-preferred choice (grey) on correctly performed trials but not on incorrectly performed ones (errors). (B) Cells in the granular OFC, by contrast, encode the choice significantly on both correct and error trials. (C) The same conclusion arises from an analysis of the receiving operating characteristic (ROC) of cell activity, which measures the ability of an ideal observer to detect the choice on each trial based on a cell's activity level. Note that the ROC value falls to 0.53 for error trials in the mid-lateral PF cortex, which corresponds to chance levels. Abbreviation: sp/s, spikes per second. From Tsujimoto S, Genovesio A, Wise SP. Comparison of strategy signals in the dorsolateral and orbital prefrontal cortex. *Journal of Neuroscience* 31:4583–92, © 2011, The Society for Neuroscience.

which involved the granular parts of area 14, did not impair the ability of the monkeys to assign credit to choices. Lesions of the lateral OFC caused this impairment.

Lesions of area 14 caused a different impairment. Monkeys with these lesions made suboptimal choices when the value of the ‘newly best’ and ‘previously best’ stimuli differed by small probabilities. The value of the third stimulus in relation to the ‘newly best’ stimulus also influenced their choice. Noonan et al. concluded that the medial OFC

contributes to comparing the value of different outcomes, after they have been assigned to particular choice stimuli. They suggested that it does so in terms of a ‘common currency’, that is, a unidimensional representation of value as discussed earlier.

Neuroimaging studies support these ideas. The studies reviewed earlier by O’Doherty et al. (2001) and by Kim et al. (2011) pointed to activation in area 14 in relation to outcomes of many kinds, as expected for a ‘common currency’ representation of value.

In another imaging study, Noonan et al. (2011) gave people the choice among objects. The outcomes consisted of visually presented gift certificates that the subjects could use later. One kind of certificate could be used to buy music and videos, another kind books, a third food at a café, and so forth. In one condition, a given choice always led to a particular kind of gift certificate; in another condition, a given choice produced a random outcome. The subjects thus learned the associational mappings between their choice and a particular type of outcome in the former condition but not in the latter one.

Noonan et al. found an activation in the lateral OFC as people assign the credit for an outcome to a specific choice, whereas they found an activation in the medial OFC when people used the outcome values in order to guide choices. Specifically, they found greater activation in the lateral OFC when there was a consistent relationship between a given choice and a type of outcome. In this circumstance, the lateral OFC increased its coupling with areas that represent objects, such as the perirhinal cortex, as well as with brain structures that contribute to updating motivational valuations, such as the amygdala.

By contrast, Noonan et al. found a different pattern of activation in the medial OFC. Activation there did not reflect whether the outcomes informed people about specific choice–outcome mappings. Instead, it was proportional to the value of predicted outcomes. This finding agrees with those that Noonan et al. (2010) obtained in monkeys with medial OFC lesions.

These findings roughly match those from neurophysiological studies. In the lateral OFC, cells encode visual stimuli that indicate the value of an outcome, rather than the level of thirst per se (Bouret & Richmond 2010). Although some cells in the lateral OFC showed a decrease in activity as monkeys became sated on a reward, in agreement with the results of Critchley and Rolls (1996), this property occurred more commonly among cells in the medial part of the orbital PF cortex (Bouret & Richmond 2010). This finding is consistent with a role of area 14 in comparing outcome values in a ‘common currency’ based on a current motivational state.

Brodersen et al. (2011) distinguished between the same areas in an imaging study in which subjects performed the three-arm bandit task (Figure 4.5B). Subjects chose among stimuli, which generated probabilistic outcomes. These outcomes provided feedback about each choice in three conditions: on the same trial, delayed by one trial, or delayed by a random number of trials. In either of the first two conditions, the subject could assign outcomes to previous choices, but in the third they could not.

Brodersen et al. found more activation in the lateral OFC in either of the first two conditions than in the third, random condition. They concluded that the activation reflected whether their subjects could assign causal responsibility between an outcome and a

specific choice. Their results also ruled out the possibility that their activations reflected the outcome in any simple way or that it reflected reward-prediction errors.

These finer subdivisions have a parallel in the devaluation and extinction experiments discussed earlier. Recall that lesions of the granular OFC cause an impairment on the devaluation task. Lesioned monkeys do not make choices in accord with current needs. Monkeys with the same lesions also show slower ‘extinction’ learning than normal. Rudebeck and Murray (2011) made selective lesions of the lateral OFC (corresponding to areas 11 and parts of area 13) and found that they caused the full impairment in the devaluation task. An independent study obtained similar results (Machado & Bachevalier 2007).

Lesions of the medial OFC, including area 14, did not affect choices on the devaluation task. Instead they caused a mild impairment on the extinction task, which lesions of the lateral OFC left unaffected. The same lesion also affected choices on a value-based transitivity test. In this test, monkeys chose between objects that have been associated with different familiar foods, among which they have a ranked preference. Monkeys with medial OFC lesions (area 14) made more choices that violated their overall food preferences than did normal monkeys, but monkeys with lateral OFC lesions (areas 11 and 13) did not show this effect (Rudebeck & Murray 2011).

There are two ways to look at the results from the devaluation task in relation to the learning of choice–outcome associations. According to one view, the lateral OFC performs two related functions. It learns choice–outcome mappings, and it updates the motivational valuations of the outcomes based on current biological needs.

Alternatively, the impairment might result entirely from a difficulty in learning the associative mappings. On this view, an inability to assign distinct outcomes to object choices correctly might cause the deficits on the devaluation task, especially when the monkey needs to learn many associations between choices and outcomes. Perhaps monkeys with lateral OFC lesions can learn that an object is associated with reward in a general sense, but because they are slow to learn the association between objects and the sensory properties of particular rewards, they do not know which reward that might be.

Against the latter interpretation is the fact that, in the devaluation task, monkeys do not need to learn new associations between objects and foods: they seem to have learned these mappings before the key test sessions. Yet they still show devaluation effects. Although this finding does not decide the issue entirely, we favour the view that the lesion effects on the devaluation task and credit-assignment tasks reflect two aspects of the choice–outcome relationship. One aspect involves learning what choice caused a given outcome, and the other involves knowing what that outcome is worth at the time of the choice.

Summary

To summarize what we say about the granular OFC, we review evidence that it plays a specialized role in biasing choices among objects and other stimuli. It does so by using past experience to predict the outcome that is likely to follow a given choice, as updated in terms of current biological needs. It also evaluates rules based on objects, such as

matching by colour or by shape. All of this depends, in part, on external sensory signals and their interaction with ‘internal’ motivational signals reflecting current needs.

The function of the orbital PF cortex complements that of the medial PF cortex, which biases the choice among actions and rules for action (Chapter 3). These choices depend primarily on ‘internal’ signals, such as those that represent actions, the memory of previous events, and current needs. This does not mean, however, that the medial PF cortex has no representation of object valuations. It does. And we review evidence from imaging and cell recording that indicates a role for the medial PF cortex in actions related to objects.

A key set of findings shows that the granular OFC plays a key role in improved credit assignment. In performing this function, it learns, represents, and updates the causal relationship between the choice of a particular object and the specific outcome caused by that choice, and it can do so on the basis of a single event.

Finally, different parts of the granular OFC have dissociable functions. The medial part assesses outcomes in terms of an abstract, one-dimensional representation of value called a ‘common currency’. By contrast, the lateral part represents outcome in their many dimensions based on extensive feature conjunctions (Figure 4.3).

Conclusions

How the orbital PF cortex can do what it does

The connections of the orbital PF cortex (OFC) explain how it performs its functions. First, it receives sensory information from several sensory modalities. As a result, the OFC can represent conjunctions of features, for example the sight and flavour of food (Figure 4.3). Second, the orbital PF cortex has connections with the amygdala, which updates the motivational valuation of choices in terms of current biological needs. Through its interactions with the sensory cortex and the amygdala, the orbital PF cortex learns about choices among objects and the outcomes that follow from those choices. We can summarize these and some additional points as follows:

1. The agranular OFC has connections with the olfactory, gustatory, and visceral cortex, which enable them to represent specific sensory outcomes—specific smells and tastes, for example.
2. The orbital PF cortex has extensive interconnections with the medial PF cortex. The medial PF cortex biases choices among actions and rules regarding action (Chapter 3), and the orbital PF cortex improves choices among stimuli and rules regarding stimuli, such as matching to colour or shape. We thus relate the medial areas to ‘internally’ guided behaviour and to the choice of actions directly, as opposed to the choice of objects to act upon. Likewise, we relate the orbital areas to externally guided behaviour and choices among objects. Foraging choices involve both, and this fact explains why the medial and orbital PF cortex must interact.
3. The orbital PF cortex has extensive interconnections with the basolateral amygdala, which underlie the updating of outcome valuations based on current biological needs.

The evidence from monkeys shows that the lateral part of the granular OFC subserves this kind of updating function. As a result, the value of a particular food or fluid depends on how much of it an animal has recently consumed. The agranular OFC also has connections with the amygdala, so we assume that a similar updating function applies to both rodents and primates and to both the granular and agranular OFC. More research is needed on this topic, however.

4. The granular OFC has strong connections with the inferior temporal and perirhinal cortex, which provide information about objects, including their colour, visual texture, glossiness, translucence, and shape. They also receive somatosensory inputs, especially from the mouth and tongue representations. When combined with point 1, these connections permit primates to construct representations of specific foods and fluids with a much higher dimensionality and greater specificity than could their ancestors. These advances reflect the visual specializations of primates (Chapter 2).

Taken together, these connections explain the unique functional capabilities of the primate OFC and account for its key role in improved credit assignment. The ability to use a single event to assign a choice to an outcome depends in large part on the rich, high-dimensional representations that the primate visual system provides.

Proposal

In Chapter 3 on the medial PF cortex, we begin to develop a proposal that culminates in Chapter 8. Here we do so for the orbital PF cortex, in both brief and expanded forms.

In brief:

The orbital PF cortex contributes to evaluating and choosing among sensory stimuli based on associations with outcomes, in relation to current needs.

Expanded:

The orbital PF cortex contributes to the function of the PF cortex, as a whole, by biasing the choices among sensory stimuli and rules based on stimuli. It does so via an evaluation of specific expected outcomes, as evaluated in terms of current needs. In primates, it can learn which choice among stimuli caused a particular outcome based on a single event. It can both compare outcomes in a common currency and contrast specific outcomes with each other.

Why other areas cannot do what the orbital PF cortex does

We also need to explain why only the orbital PF cortex can do what it does. Other cortical areas also have a degree of convergence from two sensory modalities, sometimes more, and thus have been called polymodal or multimodal. Superior temporal areas such as the superior temporal polysensory area (STP) (also called area TPO) fall into this category (Seltzer & Pandya 1994), along with other regions at the boundaries between predominantly visual, auditory, and somatosensory domains, such as area VIP in the posterior parietal cortex (Schlack et al. 2005).

But none of these areas have the degree of feature conjunction and modality convergence that the orbital PF cortex has, especially in primates. This means that they cannot construct conjunctions of the sort that Figure 4.3 illustrates. At the same time, areas such as the posterior parietal cortex lack the connections with the amygdala that the OFC has, and therefore they cannot as readily relate the visual information that they process to value based on current biological needs.

Contribution to foraging choices

The massive convergence of sensory modalities in the OFC permits mammals to link specific outcome representations to stimuli in order to improve their foraging efficiency. Thus mammals can make choices based on more sophisticated distinctions among foods or fluids than could their nonmammalian ancestors, and primates can do so based on yet more sophisticated distinctions compared to their nonprimate ancestors and to most other modern mammals.

Although the ability to make finer sensory distinctions among outcomes is important, we think that the concept of credit assignment explains the most about PF cortex function. The fact that animals make foraging choices based on predicted outcomes makes it advantageous to accurately assign past outcomes to the choices that have produced them. All foraging animals face this problem, of course, but Chapter 2 explains that early primates adapted to a fine-branch niche, where they foraged in dim light among a clutter of potential food and non food items. The granular OFC evolved in these animals, as they adapted to this niche. This chapter reviews evidence that these areas provide the current value of each object in terms of the animal's current needs.

We propose that, compared to their ancestral condition, these early primates could make improved credit assignments based on a single event and that the newly evolved, granular OFC enabled that advance. Modern monkeys with lesions of the granular OFC can still learn by integrating information over many past trials, as rats and other mammals do, but they cannot attribute an outcome to a single event. We take this finding to be critical in understanding the function of the PF cortex, and we return to it in Chapter 8. There we contrast the ability to learn from a single event with the slower, cumulative learning that eventually optimizes foraging choices, but takes longer to do so. Without the improvements in causal analysis provided by the granular OFC, monkeys revert to an approximation of the capabilities that other mammals have. Chapter 8 develops this idea in the context of PF function, considered as a whole.

This chapter also reviews evidence that different subdivisions of the granular OFC contribute differently to the choices that primates make among objects. The lateral part of the granular OFC helps primates answer two key questions: what specific food or fluid does a given choice produce?; and, as assessed in terms of current needs, what is that outcome worth? The medial part of the granular OFC helps them answer a third question: as transformed into a one-dimensional representation of value, a 'common currency', how does this choice compare with other options?

We can summarize this anatomical distinction in either of two ways. First, the lateral OFC learns about the value of objects and other stimuli, whereas the medial OFC mediates

choices by comparing those values (Noonan et al. 2010); second, the lateral OFC learns choice–outcome mappings that depend on *contrasts* among different outcomes, whereas the medial OFC learns choice–outcome mappings that depend on *comparisons* among different outcomes (Rudebeck & Murray 2011).

Having made their choice among objects, primates still have to find that object and maintain attention to it in a cluttered environment. The next chapter explains how the connections of the caudal PF cortex support its role in these search and attentional functions.

Chapter 5

Caudal prefrontal cortex: searching for goals

Overview

The caudal PF cortex contributes to the visual search for objects such as food and signs of food through both overt attention (eye movements) and covert attention, and its connections explain how it can perform these functions. The caudal PF cortex, which includes the frontal eye field (FEF), has connections with both the dorsal and ventral streams of the visual cortex and with brainstem oculomotor nuclei. Overt attention depends on its connections with brainstem oculomotor nuclei, both directly and indirectly via both the superior colliculus and the basal ganglia. Covert attention depends on enhanced sensory responses that are mediated through interactions with the visual cortex, among other sensory areas. Along with granular parts of the orbital PF cortex, the caudal PF cortex evolved in early primates (Chapter 2). Together, these two new areas led to improvements in finding, attending to, and evaluating objects in the cluttered environment of the fine-branch niche.

Introduction

The previous chapter argues that the orbital PF cortex assigns a value to objects, as assessed in terms of current biological needs. This chapter proposes that the caudal PF cortex searches for those objects, and that it does so both by covert attention to peripheral targets and by orienting the eyes towards them.

Much of this chapter deals with vision and eye movements, which evolved very early in vertebrate history. Evidence for eyes and extraocular muscles occurs in the oldest vertebrate and pre-vertebrate fossils, some dating from more than 500 Ma (Shu et al. 2003). But primates made some important innovations in vision and eye movements, such as developing a fovea and trichromatic vision (Chapter 2). If we are correct that the caudal PF cortex first appeared in early primates, then it predates both the fovea and full-colour vision: an important clue concerning its function.

To understand the caudal PF cortex, we need first to see how its connections permit the primate PF cortex to search for objects such as food, using both eye movements and covert attention.

Areas

In macaque monkeys the caudal PF cortex refers to the cortex that lies immediately rostral to the genu of the arcuate sulcus. Figure 5.1 sketches its location.

As we define it, the caudal PF cortex always includes area 8 and, for the purposes of this chapter, it also includes the caudal part of the principal sulcus in macaque monkeys. We justify this grouping by noting that, just as in area 8 (Chafee & Goldman-Rakic 1998), the majority of the cells in the caudal part of the principal sulcus modulate their activity in relation to eye movements (Tanila et al. 1993). Petrides and Pandya (1999) recognized an area that they call 9/46 that lies around the caudal end of the principal sulcus, and they distinguished this area both from the rostrally adjacent mid-lateral PF cortex (area 46) and the dorsomedial area 9. As the name indicates, Petrides and Pandya see area 9/46 as having cytoarchitectonic properties that resemble both area 9 and area 46, and all three areas have a granular cytoarchitecture. We call the cortex in the caudal aspect of the principal sulcus the *postero-lateral PF cortex* (Figure 1.4) and include it in the caudal PF cortex for now. We acknowledge, however, that one could include it in the dorsal PF cortex (Chapter 6) without violating any anatomical principle. Table 1.2 uses a query mark (?) to denote these two options. Accordingly, many of the points made in relation to the postero-lateral PF cortex pertain to both this chapter and the next one.

In macaque monkeys, saccadic eye movements can be evoked by microstimulation of the rostral bank of the arcuate sulcus, near the caudal end of the principal sulcus (Bruce et al. 1985), and this property defines the frontal eye field (FEF). Higher currents can, through current spread, evoke saccades from a wider area (Robinson & Fuchs 1969), but it is generally accepted that the low-threshold region corresponds to the FEF. Area 8 thus

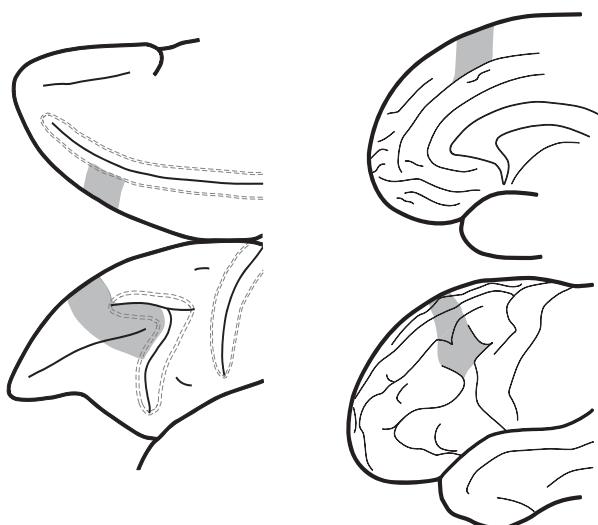


Fig. 5.1 The caudal PF cortex in the macaque monkeys (left) and humans (right). Format as in Figure 1.2.

includes the FEF, which varies from the typical granular cytoarchitecture towards the dysgranular (Stanton et al. 1989).

Amiez and Petrides (2009) have reviewed studies that have localized the FEF in the human brain by electrical stimulation. Saccades can be evoked with low threshold stimulation from an area that lies just rostral to the superior precentral sulcus, as well as from stimulation over that sulcus. Amiez et al. (2006) used imaging methods to locate the peak of activation with respect to the cortical anatomy of individual subjects. The FEF, as so defined, was located consistently in the ventral branch of the superior precentral sulcus, and this location agrees broadly with the location as defined by electrical stimulation. Amiez and Petrides (2009) present maps for macaque monkeys and humans and show that in both cases the FEF can be distinguished from the premotor cortex, from which electrical stimulation also evokes eye movements.

Microstimulation has also identified a second eye field in the frontal lobe of macaque monkeys: the supplementary eye field (SEF) (Schlag & Schlag-Rey 1987). As in the FEF, cells in the SEF increase activity before saccades (Hanes et al. 1995). In macaques, the SEF lies in the dorsomedial frontal cortex, within area 6 (Schlag & Schlag-Rey 1987; Olson & Gettner 1999), and it has a similar location in the human brain (Amiez & Petrides 2009).

Connections

Figure 5.2 shows a summary of selected corticocortical connections of the caudal PF cortex, including the FEF, in macaque monkeys. These data come mainly from Petrides and Pandya (1999), who injected tracers into subdivisions of area 8 (areas 8B, 8Ad, or 8Av) and described their connections. This study has the advantage over earlier ones (Petrides & Pandya 1984; Barbas 1988; Barbas & Pandya 1989; Cavada & Goldman-Rakic 1989) in that Petrides and Pandya (1999) made small and relatively selective injections.

The pattern of connections leads to the following conclusions:

1. Area 8Ad, area 8B, and the postero-lateral PF cortex connect with areas that perform oculomotor and visuospatial functions. For example, they have connections with area LIP, which lies in the intraparietal sulcus (Cavada & Goldman-Rakic 1989; Andersen et al. 1990), and cells in LIP encode eye movements (Snyder et al. 1997). The same PF areas have connections with area PG of the inferior parietal cortex (Cavada & Goldman-Rakic 1989), and many of the cells in that area encode eye orientation (Sakata et al. 1980). Finally, area 8Ad has connections with temporal area MST, where cells respond to the motion of visual stimuli (Celebrini & Newsome 1995).
2. These visual areas make up part of the dorsal visual stream (Ungerleider & Mishkin 1982; Milner & Goodale 2007), as distinguished from the ventral visual stream. As a general statement, the dorsal stream includes posterior parietal areas that process information about the spatial targets of action, and the ventral stream includes inferior temporal areas that process information about the colour, shape, and texture of visual stimuli.

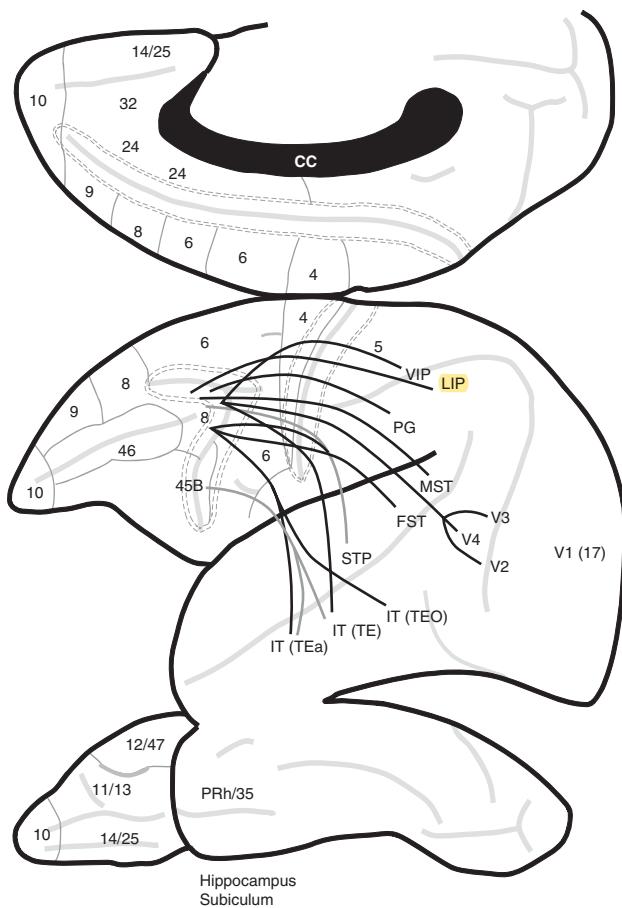


Fig. 5.2 Selected connections of the caudal PF cortex. Figures 1.4 and 1.5 give the names of sulci and areas. Lines connect some of the areas that have direct axonal connections with the caudal PF cortex, assumed to be reciprocal unless otherwise stated.

3. The **FEF** receives information from early (low-order) visual areas, such as occipital visual area V2 and V3 (Stanton et al. 1995), but area **8Ad** and the postero-lateral PF cortex do not. The FEF thus receives less highly processed visual information than other parts of the caudal PF cortex and than other parts of the PF cortex.
4. Area **8Av** differs from **8Ad**, area **8B**, and the postero-lateral PF cortex in having connections with the ventral stream as well as with the dorsal stream. Area **8Av** has connections with the area **TEO** (Webster et al. 1994), as well as with other parts of the inferior temporal cortex, such as the cortex in the inferior bank of the superior temporal sulcus (Petrides & Pandya 1999).
5. The component areas of the caudal PF cortex have dense interconnections with each other. Areas **8Ad** and **8Av** have reciprocal projections with each other and with the postero-lateral PF cortex (area **9/46**). These interconnections support our inclusion

of the postero-lateral cortex in this chapter. As depicted in Figure 1.8, the caudal PF cortex as we define it closely resembles the caudal network as defined by Price and Drevets (2010).

Figure 5.2 and the previous list deal with corticocortical connections, but the corticofugal connections of the caudal PF cortex also explain something important about its function:

1. The FEF (Künzle, 1976; Huerta et al. 1986), the remainder of area 8 (Fries 1984), and the postero-lateral PF cortex (Selemon & Goldman-Rakic 1988) all send a direct projection to the superior colliculus. The superior colliculus and its homologues function in all vertebrates to orient sensory receptors on the head. So these corticofugal connections point to a role of the caudal PF cortex in controlling eye movements, but many other parts of the cerebral cortex also project to the superior colliculus (Leichnetz et al. 1981; Fries 1984), so this anatomical feature does not distinguish the PF cortex from other areas.
2. The FEF can also influence activity in the superior colliculus via projections to the basal ganglia. The FEF projects to the medial part of the caudate nucleus (Stanton et al. 1988), which in turn projects to the substantia nigra, pars reticulata (Hedreen & DeLong 1991). This nucleus projects to the superior colliculus, where it exerts an inhibitory influence (Hikosaka & Wurtz 1985).
3. Finally, the FEF projects directly to the brainstem oculomotor nuclei (Segraves 1992; Yan et al. 2001).

Summary

The connectional fingerprint of the caudal PF cortex indicates that it receives direct, low-order visual inputs, that it has a dorsal–ventral distinction that parallels the dorsal and ventral visual streams, and that it has outputs to oculomotor nuclei both directly and indirectly via projections from the basal ganglia to the superior colliculus.

The FEF as a prefrontal area

Despite having outputs that point to a role in controlling eye movements, we do not view the FEF as functioning primarily in oculomotor control. We know that when pharmacological agents inactivate the FEF, visually guided saccades become inaccurate when directed into contralateral space (Sommer & Tehovnik 1997). In this sense, the FEF resembles the premotor cortex. For example, inactivation of the ventral premotor cortex causes inaccurate limb movements (Kurata & Hoffman 1994).

We also know that permanent lesions of the FEF **do not abolish saccadic** eye movements, just as premotor lesions do not abolish limb movements. However, one reason is that both the SEF (Huerta & Kaas 1990) and the parietal area LIP (Holloway 2002), among other areas, also send projections to the **superior colliculus**. So in order to abolish saccades one needs to remove both the superior colliculus and FEF together (Schiller et al. 1979, 1987). Only the smallest saccades remain.

Yet, in spite of this evidence of motor functions, we view the FEF as a prefrontal area and not a premotor area. We do so because we distinguish between the mechanisms for generating, finding, and attending to goals and the mechanisms for achieving them. Remember that by the term goals we refer to objects or locations, and not to rewards or outcomes. Actions that achieve goals produce outcomes. Except in the laboratory, visual fixation and attention can never produce an outcome in this sense. In the wild, looking at or otherwise attending to a food item does not produce any nutritional or hydration benefit. It takes other mechanisms to achieve this desired outcome. We see the former as being a function of PF cortex and the latter as being the province of premotor cortex.

In their treatment of the premotor cortex, Shadmehr and Wise (2005) suggested that it deals with the visuomotor transformations which convert the visual target of a reaching movement into the changes in joint angles and forces that drive the hand to those targets. Chapter 2 mentions this mechanism. The details are available in Shadmehr and Wise, but a brief summary will help here.

Consider someone reaching for a coffee cup. Basically, the motor system needs to establish two locations: the target location and the initial position of the hand. Shadmehr and Wise proposed that cells in the posterior parietal and premotor cortex encode these locations in a coordinate frame that has, at its origin, the visual fixation point. In theory, however, any retinal coordinate will do as the origin. Figure 5.3 shows how this mechanism could work. The figure shows two vectors: one with its tail at the fixation point and its tip at the movement target; the other with its tail at the fixation point and its tip at the

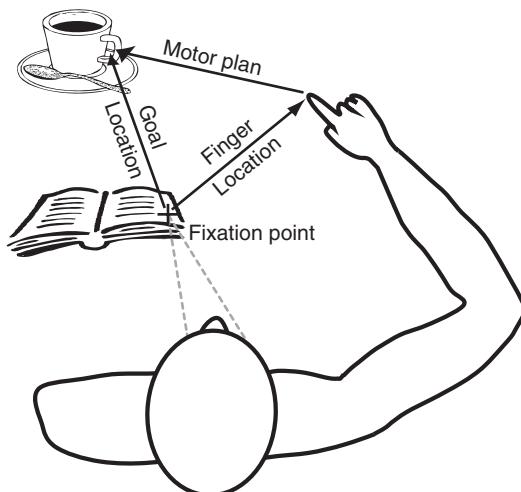


Fig. 5.3 Vectorial representation of a motor plan. The person's goal is to put the tip of his finger through the handle of the coffee cup. He or she develops a plan to do so while reading a book. + marks his fixation point at that time. Two vectors that originate from the fixation point encode the location of the goal and the current position of the finger in an allocentric, extrinsic coordinate frame: fixation-centred coordinates. The difference between the two vectors represents the motor plan in hand-centred coordinates. Modified from Shadmehr R, Wise SP. *The Computational Neurobiology of Reaching and Pointing: A Foundation for Motor Learning*, © 2005 Massachusetts Institute of Technology, by permission of The MIT Press.

current position of the hand. A simple subtraction of the two vectors yields a vector with its tail at the hand and its tip at the target. The result of this computation amounts to a ‘motor plan’ that converts a visual frame of reference to a hand-centred coordinate frame. The premotor and primary motor areas, along with subcortical structures, convert this vector into the joint-angle changes and forces that make this movement.

Through this mechanism or one like it, the premotor and posterior parietal areas achieve goals in a way that neither eye movements nor other forms of attention ever can. The person in our example wants coffee and so directs his or her attention to the cup. Attention can either be overt, which means orienting the fovea toward the cup, or it can be covert, which means attending to the cup without looking at it. Something about the contents of the cup has a value in relation to the person’s current needs, and therefore he or she generates a goal—the coffee cup—then searches for and orients attention to the cup. We propose that the caudal PF cortex performs the search and attentional function. Although visual fixation and attention cannot achieve the desired outcome, reaching to the cup, bringing it to the mouth, and drinking from it can. We view these latter functions as the province of the premotor and primary motor areas, among other parts of the motor system.

So what is the evidence that the FEF is involved in the search for and attention to goals rather than the means of achieving them? We have already seen that, unlike the premotor areas, the FEF receives direct inputs from low-order visual areas, specifically the areas of occipital and temporal cortex called V2, V3, V4, and MST (Stanton et al. 1995). These connections explain why some cells in the FEF show increased activity after the presentation of sensory stimuli, but not before movement (Schall 1991). They seem to specify visual goals and not the eye movements needed to fixate these goals. Furthermore, of the cells that project to the FEF from parietal area LIP, 78% have visual responses but no saccade-related activity (Ferraina et al. 2002). This projection could provide another source of information concerning visual goals, and one that is independent of motor commands.

Of course, many of the cells in the FEF have visuomotor activity: they modulate their activity both when the visual target appears and before an eye movement (Schall 1991). Many of them specify the location of the stimulus soon after it appears, when it attracts attention. Sato and Schall (2003) taught monkeys to detect a visual pop-out stimulus in an array of distractors, and then to make a saccade either to that location (prosaccade trials) or to a saccade target in the opposite direction (antisaccade trials). If the activity reflected the location of the stimulus, it should be the same on the two trial types.

Sato and Schall compared the activity of FEF cells for the two tasks when the pop-out stimulus fell into a cell’s receptive field. For the antisaccade task, note that when the pop-out stimulus did so the saccade target was in the opposite direction. Yet, the activity of 57% of the task-related cells initially reflected the location of the stimulus, although subsequently 86% of these cells later coded for the target of the saccade.

These results show that cell activity in the FEF can reflect the location of a stimulus, independent of movement, and this activity reflects the orientation of covert attention. In agreement with this suggestion, Armstrong and Moore (2007) showed that intracortical

microstimulation of the FEF enhances the response of cells in visual area V4, a mid-level area of the ventral visual stream. And it does so specifically for a particular part of visual space. The effect of stimulating the FEF probably mimics what happens when monkeys attend covertly to an object in that location.

If the FEF genuinely functions in covert attention, as well as overt attention, temporary inactivation within this area should lead to an impairment in attention to extrafoveal stimuli. So Wardak et al. (2004) taught monkeys to detect a target in a field of distractors, while the animals maintained fixation on a central spot of light. After inactivation of the FEF, the monkeys were slow to detect the peripheral target. Iba and Sawaguchi (2003) showed that inactivation also caused monkeys to be slow to make saccades to the target. These findings suggest that the FEF functions in both overt and covert attention to stimuli, especially when these stimuli serve as goals for subsequent actions.

This suggestion fits well with the account given in Chapter 2 of prefrontal evolution. Strepsirrhine primates lack a fovea, and early primates probably lacked one, as well. Because the caudal PF cortex, including the FEF, evolved in early primates, it could not at first have had anything to do with the fovea or foveation. So, in this sense, all vision in these animals corresponds to extrafoveal vision and all attention is covert. Smooth-pursuit eye movements allow anthropoid primates to lock the fovea and overt attention onto moving objects and maintain that high-resolution image. But this capacity, too, probably evolved in primates that lacked a fovea (Shepherd & Platt 2010). Thus, it is a mistake to look to foveal vision or overt attention in accounts of the origins of the primate PF cortex, in general, or of the caudal PF cortex, in particular.

Nevertheless, the fovea did eventually evolve in later primates, and modern tarsiers, monkeys, apes, and humans (haplourhines) have it by inheritance. Despite its many advantages, the ability to foveate comes at a price. What about the remainder of the visual world? That cluttered world contains many other salient items. In a sense, a fovea-free retina provides a more balanced view of the world. The advantage of retaining covert attention, even after the evolution of the fovea, is that it allows enhanced processing of a limited number of extrafoveal items, even as the most intensive processing is devoted to foveated items and places. The importance of covert attention and search lies in the possibility that all attended objects, and not just foveated ones, might become goals for future actions. According to this view, the caudal PF cortex, including the FEF, evolved for covert search and attention, but later adapted to overt attention once the fovea appeared.

Summary

Many neuroscientists view the FEF as an oculomotor area and treat it as a premotor area for eye movements. We suggest a different idea. We view the FEF and the other parts of the caudal PF cortex as prefrontal areas, as opposed to premotor ones, and propose that they function in the **search for** and **attention to** goals of importance to primates. In many primates, including monkeys and humans, attention to a goal usually means making an eye movement to **orient** the fovea toward it (saccades) or maintaining visual fixation on the goal as it **moves** (smooth pursuit). But covert attention also plays an important role, as it must have in early primates, which lacked a fovea. Because foveation is a form of

attention, we view eye movement as an attentional function rather than as a motor one. We propose that the caudal PF cortex, including the FEF, functions in directing either overt or covert attention to a goal, rather than as part of the mechanism for achieving goals.

Oculomotor delayed response task

We have treated the FEF separately from the remainder of the caudal PF cortex because intracortical microstimulation of the FEF evokes eye movements. But, as explained in the section on connections, the FEF has dense connections with other parts of the caudal PF cortex. Accordingly, many cells in area 8 (Chafee & Goldman-Rakic 1998) and in the postero-lateral PF cortex (Funahashi et al. 1989) have activity that is related to eye movements.

As we said earlier, the connections of the postero-lateral PF cortex lead us to consider it together with the caudal PF areas, including the FEF, in this chapter. Our discussion of cortical evolution, in Chapter 2, lends some credence to this approach, as does the presence of cells in the postero-lateral PF cortex that encode eye movements. Because of the intermediate status of the postero-lateral PF cortex (area 9/46), in this section we discuss topics that arise again in Chapter 6, most notably the issue of delay-period activity in tasks that have been called ‘spatial memory tasks’. We do this mainly for convenience and believe that nothing crucial depends on whether we classify the postero-lateral PF cortex with the caudal or dorsal groups of PF areas.

The oculomotor delayed response task has played a prominent role in studies of the caudal PF cortex, including the postero-lateral PF cortex. It differs from the classical delayed response task in that the monkey chooses among potential goals by making a saccade rather than by reaching to a spatial goal.

The oculomotor delayed response task has three phases: cue, delay, and choice (Figure 5.4). In the first phase, a visuospatial cue appears briefly somewhere in the subject’s field of view. This stimulus indicates a location towards which the monkey must direct a saccade, but until the delay period ends the monkey must continue to fixate a central light spot. After a delay period, which lasts from a few hundred milliseconds to several seconds, a ‘go’ signal tells the subject to make the saccade to the most recently cued location. Reward follows if the saccade the subject makes an accurate saccade.

Although experimenters can use any configuration of cue locations, a common version involves eight salient places arranged equidistantly in a circle centred at the fixation point, as shown in Figure 5.4. This figure shows the locations as empty squares and indicates the cue with a filled square. However, it is important to note that, as usually presented, the peripheral locations are not marked in any way, and this means that when the monkey responds to the ‘go’ signal, it makes a saccade into an unmarked location on the screen.

Many cells in the caudal and postero-lateral PF show delayed period activity during this task (Chafee & Goldman-Rakic 1998). Figure 5.4 shows the memory signal as recorded from the caudal PF cortex by Lebedev et al. (2004), at the population level.

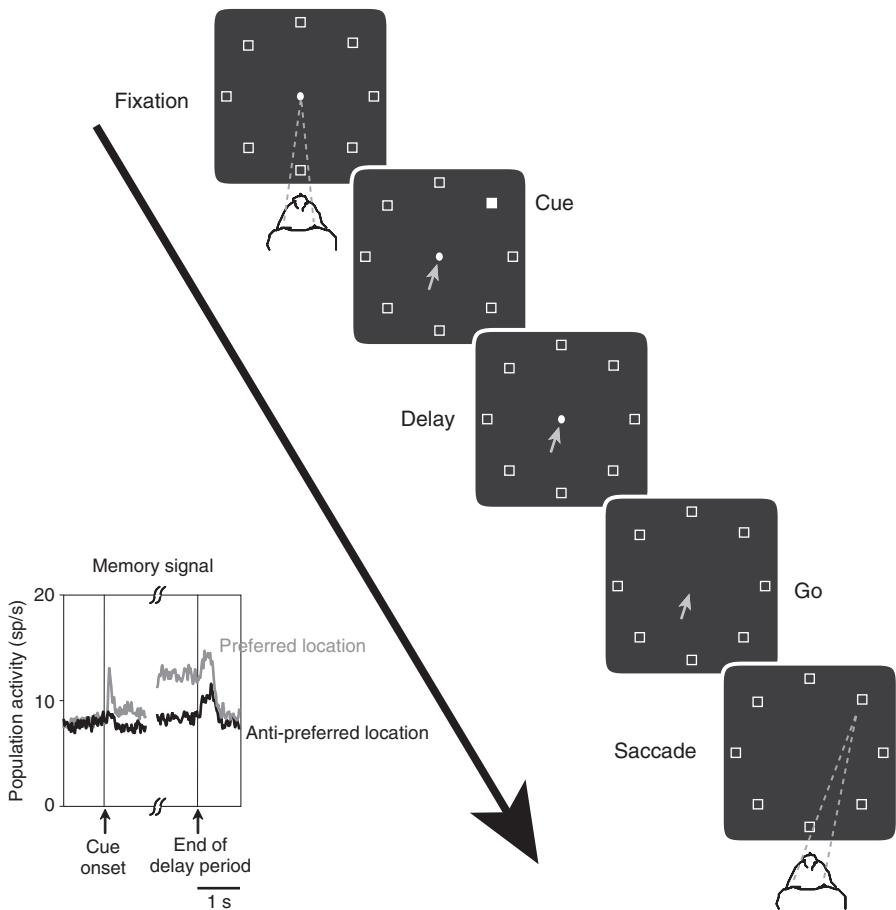


Fig. 5.4 A common version of the oculomotor delayed response task. Each panel shows the screen at a different time during a trial, with unfilled white squares as potential spatial targets on other trials. The filled white square illustrates the cue for an example trial, and a filled white circle indicates the fixation point. Grey dashed lines and grey arrows show the monkey's fixation point. The inset at the lower left shows the spatial memory signal, recorded from a population of PF cortex cells by Lebedev et al. (2004), with the average activity for the preferred memory location in grey and that for the anti-preferred location in black. Because Lebedev et al. controlled for attention, these data represent the strongest evidence for spatial memory signals in the PF cortex, although they occur only in a minority of the cells that encoded locations during the delay period.

Funahashi and his colleagues (Funahashi et al. 1989; Takeda & Funahashi 2002) present diagrams of the sites at which their electrodes penetrated the cortex, and we assume that these cells extended throughout the sampled region. Lebedev et al. show that cells with memory-specific signals lie in the caudal 9 mm of the principal sulcus, mainly in and near its dorsal bank. Chafee and Goldman-Rakic (1998) reported that delay-period activity comes mainly from area 8A, but their diagram show that some of the cells come from the postero-lateral PF cortex, as well.

Imaging experiments yield results in similar areas. Inoue et al. (2004) compared activations for saccades made in the oculomotor delayed response task with activations on a task in which the monkeys made saccades to locations marked on a screen. The differential activation lay in the postero-lateral PF cortex and area 8, including the FEF.

This is an important observation in view of the fact, explained in the next chapter, that performance on the classical, reaching version of the delayed response task depends on the mid-lateral PF cortex and not on the caudal PF cortex. The oculomotor delayed response task thus differs from the classical delayed response task, and conclusions based on the oculomotor version task do not necessarily apply to the classical delayed response- or delayed alternation tasks. The lack of effect from postero-lateral PF lesions on the classical version of these tasks (Butters & Pandya 1969) reinforces the idea that this area plays a role in the search for and attention to goals rather than in either their achievement (a premotor cortex function) or their generation (a dorsal PF cortex function, as Chapter 6 proposes).

Interpreting delay-period activity

The traditional interpretation of delay-period activity in the oculomotor delayed response task, as in the standard version of the delayed response task, is that it reflects retrospective spatial working memory. On this view, the activity reflects the maintenance of a cue location in short-term memory. This interpretation partly comes from calling the task a ‘spatial memory task’ and thus assuming that the principal cognitive process that occurs during the delay period is the maintenance of sensory information. And indeed, proponents of this view often call the delay period a ‘memory period’. However, Chapter 1 warns against accepting the names given to tasks. The fact is that other processes also occur during the delay period, including covert attention to the cued location and preparation of the movement.

There are several methods for trying to distinguish among these possibilities, and we have numbered them:

1. One can compare two versions of the oculomotor delayed response task. Thus, Funahashi et al. (1993b) compared one version in which the monkey had to make a saccade to the target (a prosaccade), with another version in which the monkey had to make a saccade to the location 180° from the cue (an antisaccade). In a later study, Takeda and Funahashi (2002) compared the standard oculomotor delayed response task with a condition in which the monkeys had to make a saccade at 90° to that location.

These experiments have the following logic: if the delay-period activity encodes the cue’s location in memory, then it should be the same regardless of the goal of the movement. In both studies, the majority of task-related cells reflected the location of the cue, although a substantial minority reflected the location of the goal. Funahashi et al. reported that 31 out of 51 (61%) of the task-related cells encoded the location of the cue, whereas 13 of these 51 cells encoded the location of the goal. Despite this small sample of cells, these findings led the authors to conclude that the delay-period activity reflected the memory of the cued location.

- The second method attempts to exclude the possibility that the activity encodes non-sensory factors by using a single, repetitive hand movement to report the cue's location, rather than a movement to that location. Sawaguchi and Yamane (1999) used this approach. They presented a spatial visual cue after the delay period and required the monkey to release a lever only if it matched the location of the cue. Readers will recognize this as a spatial version of the matching-to-sample task. Of the task-related neurons, 48% showed delay-period activity and, of these cells, 90% encoded the cued location. These results have also been taken to support an interpretation of delay-period activity in terms of spatial memory.
- The two methods just described can be combined, as in an experiment by di Pellegrino and Wise (1993). Figure 5.5 illustrates the experimental design. As in the experiment

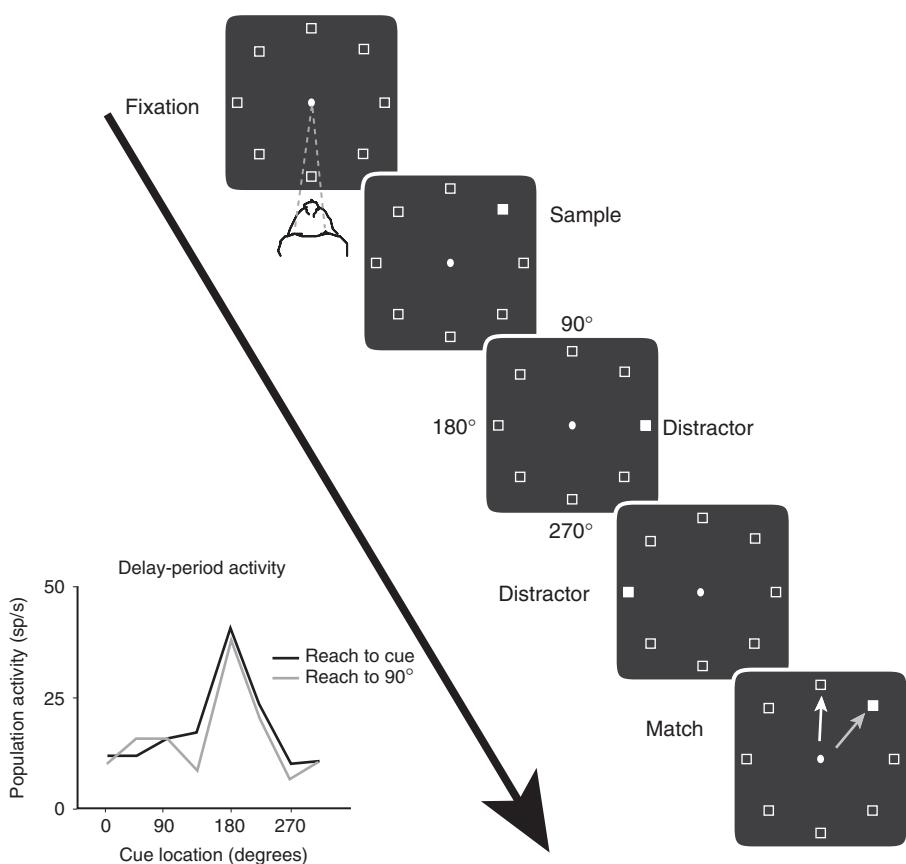


Fig. 5.5 Spatial matching-to-sample task used by di Pellegrino and Wise (1993). Format as in Figure 5.4. On the bottom panel, arrows indicate the goal for a reaching movement in two conditions. In one condition, the cue location was the goal of a reaching movement; in the other condition the location at 90° (up in the figure) was always the reach target, regardless of the cue's location. The inset at the lower left shows the activity of a cell in the PF cortex that encoded the left-most cue (180°) during the delay period and did so equally in both conditions.

by Sawaguchi and Yamane (1999), the monkey needed to report whether a cue at the end of the delay period matched the location of a cue that had appeared before the delay. However, the monkeys reported the matching stimulus in different ways, illustrated by the two arrows at the bottom of Figure 5.5. This reporting requirement alternated from one block of trials to the next. In one block, the monkeys made a reaching movement to the cued location. In the next block, the monkeys reached to a fixed location regardless of where the cue and the matching stimulus had appeared. Sometimes, the angle between the cue direction and the reporting direction equalled 180°, as in the antisaccade task of Funahashi et al. (1993b) and sometimes it equalled 90°, as in the experiment by Takeda and Funahashi (2002).

Di Pellegrino and Wise recorded from caudal and postero-lateral PF cortex and found, like Funahashi et al., that 61% of their cells had the same delay-period activity regardless of the movement's goal (Figure 5.5). This result could also be taken to suggest that the activity of the cells encoded a memory of the cued location.

4. All of these studies depend on the assumption that the only two factors of importance are the location of the cue and the location of the movement goal. By calling the delay period a 'memory period', one can easily miss the alternative possibility that, along with memory, the delay period also involves attention: sometimes overt, sometimes covert. In order to test this possibility, Lebedev et al. (2004) introduced a novel experimental design, which Figure 5.6A illustrates. As Chapter 1 mentions, they taught monkeys to remember one spatial location and to covertly attend to another location, and to do so at the same time.

Lebedev et al. recorded cell activity from the caudal and postero-lateral PF cortex. Of the task-related cells that encoded a spatial location, the majority (61%) coded selectively for the attended location rather than for the remembered one. A minority (16%) of the cells coded selectively for the remembered location, and others had intermediate properties (Figure 5.6B). The attentional signal exceeded the memory signal by every measure (Figure 5.6C).

5. If the majority of cells reflect covert attention, then it should be possible to demonstrate activations when subjects need to attend somewhere but do not need to remember this location. Imaging can be used to test this prediction. Astafiev et al. (2003) cued subjects to attend to the left or right while maintaining central fixation. They reported activations in the FEF, as well as in a posterior parietal area near the intraparietal sulcus.

Curtis and D'Esposito (2006) carried out a similar imaging study, but with two delays. Their subjects saw several potential goals for a forthcoming saccade, and a first delay period followed during which the subjects needed to remember those places. During this first delay, sustained activation occurred in both the FEF and the posterior parietal cortex. An arrow then appeared to indicate which target should be the goal of an eye movement on that trial. After a second delay, the subjects made the saccade as indicated. During this second delay, sustained activation occurred only in the FEF

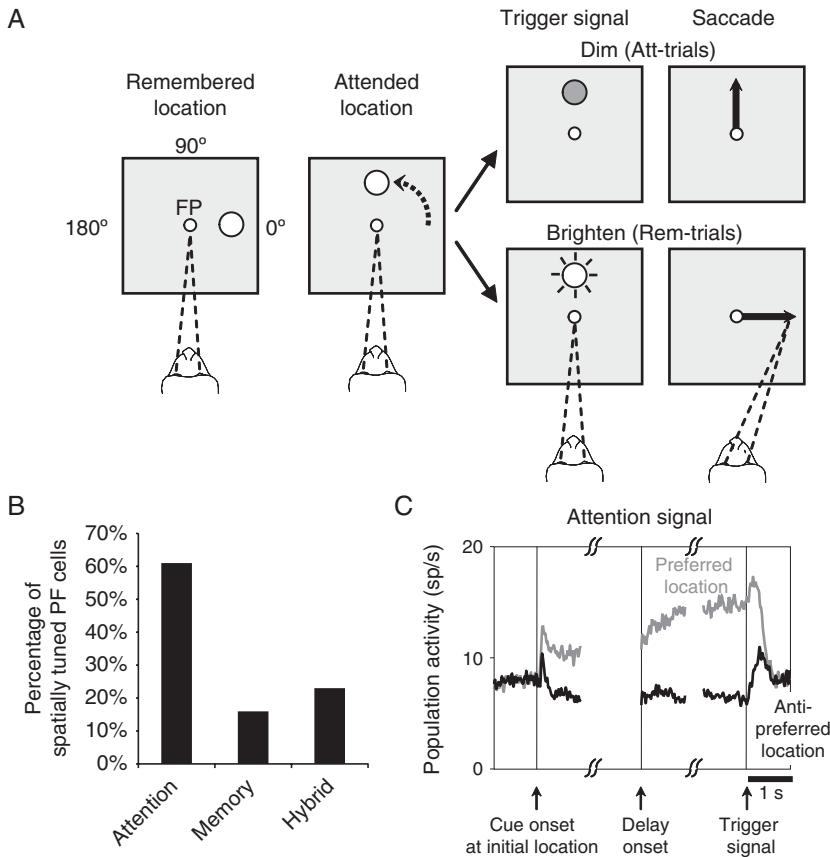


Fig. 5.6 Attention versus memory coding in the PF cortex. (A) Task design. A circle appeared on the video monitor (grey rectangle) and later began to revolve around the central fixation point (FP). It began at one of four locations and later stopped at one of the same four locations: up, down, left, and right from centre. If the circle dimmed (top fork), the monkey needed to make a saccade to the circle's final location on that trial; if it brightened (bottom fork), the monkey had to make a saccade to the circle's initial location on that trial. The arrow indicates the correct saccade in both conditions. Abbreviations: Rem, remembered-location; Att, attended-location. (B) Percentages of spatially tuned PF cortex neurons encoding the attended or remembered locations or both (hybrid). (C) Attentional signal in the format of the memory signal shown in Figure 5.4. (A) Reproduced from and (C) modified from Lebedev MA, Messinger A, Kralik JD, Wise SP. Representation of attended versus remembered locations in prefrontal cortex. *PLoS Biology* 2:1919–35, © 2004 Public Library of Science, with permission.

and not in the posterior parietal cortex. This finding agrees with the idea that foveation is an attentional function. The caudal PF cortex, including the FEF, functions in orienting attention towards potential goals, which occurred during both delay periods, not simply in remembering locations, which occurred during the first delay.

We conclude that, in these experiments, delay-period activity or activation has several possible interpretations. It could reflect a memory for the cued location, covert attention

to that location, or preparation to direct overt attention to that location. In addition, it could reflect the encoding of the task rules, a topic that we take up in the next chapter.

As a result, activity during delay periods of the oculomotor delayed response task does not demonstrate anything about retrospective spatial working memory. First, the activity could reflect covert attention rather than sensory memory. Second, the concept of working memory does not distinguish between the retrospective coding and prospective coding of locations. As we explain in the next chapter, the term prospective coding refers to short-term memories of a chosen goal. Although some experiments, such as the antisaccade task of Funahashi et al., have attempted to rule out the prospective coding of goal locations, in every case a significant minority of cells encodes the goal. And experiments pitting spatial attention against spatial memory have shown that most of the activity in the PF cortex encodes the covertly attended location and not the remembered one. We return to the topic of prospective coding in Chapters 6 and 7.

Disrupting delay-period activity

Irrespective of the correct interpretation of delay-period activity, disrupting it should cause an impairment of some sort. However, simply showing that monkeys with lesions in the caudal PF cortex do badly on a task does not demonstrate that they do so because they no longer remember the cued location. It could as well indicate that they have trouble attending to the cued location or maintaining a prospective code of it in memory.

Subjects can make two types of errors on the oculomotor delayed response task. Frank errors involve a choice of the wrong spatial goal (Keller et al. 2008), whereas accuracy errors involve a movement closer to the correct goal than to any other possible goal, but missing its exact location.

Inaccurate saccades could reflect a low-level motor disability, so one needs to compare a control condition that lacks a delay period with the standard task. Here the subject simply makes a saccade to a visible target.

Inactivation of the FEF in monkeys cause hypometric saccades. That is, the saccades to visible locations tend to fall short of the spatial goal (Dias & Segraves 1999). Hypometric saccades also occur in patients with a unilateral lesion of the FEF (Gaymard et al. 1999; Ploner et al. 1999).

Inactivation of area 8A by cooling also causes inaccurate saccades on the oculomotor delayed response task. They tend to fall short or to one side of the correct goal location (Chafee & Goldman-Rakic 2000). Inactivation of the postero-lateral PF cortex with muscimol (Sawaguchi & Iba 2001) or a dopamine antagonist (Sawaguchi & Goldman-Rakic 1991) has the same effect. And so do unilateral ablations of the postero-lateral PF cortex (Funahashi et al. 1993a) (Figure 5.7).

Although inactivation of the FEF, other parts of the caudal PF cortex, or the postero-lateral PF cortex causes inaccurate saccades, these usually head in the correct direction and end closer to the cued location than to any alternative goal. Yet, Funahashi et al. (1993a) concluded that the inaccuracy of these saccades reflected a failure of retrospective spatial working memory. They never explained how, if the monkeys could not remember

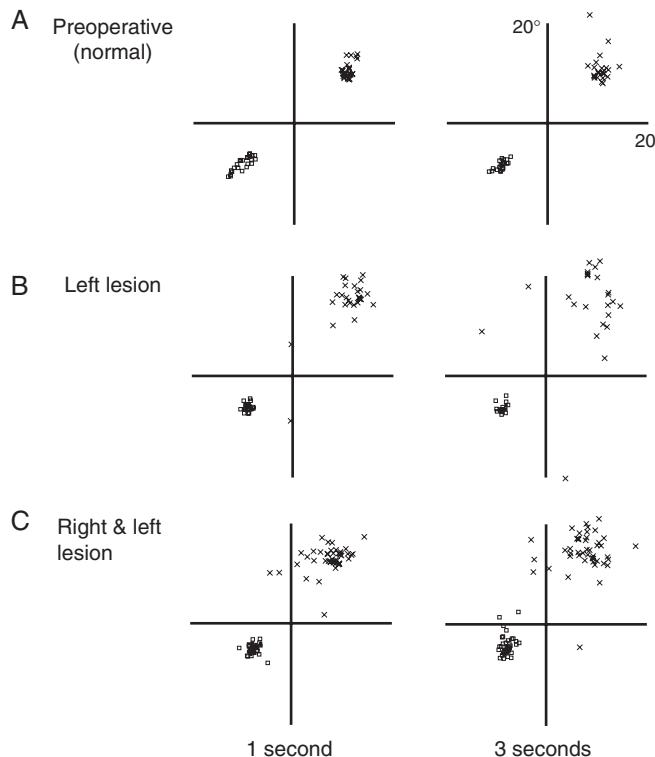


Fig. 5.7 Performance on the oculomotor delayed response task for one monkey. (A) Preoperative (normal) performance. Squares indicate the saccade endpoints for targets at 225° (down and to the left); crosses indicate targets at 45° (up and to the right). (B) Performance after a unilateral lesion of the postero-lateral PF cortex of the left hemisphere. (C) Performance after an additional lesion of the same area in the right hemisphere, in order to complete a bilateral lesion. Delay duration at bottom. Reproduced from Funahashi S, Bruce CJ, Goldman-Rakic PS. Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic 'scotomas'. *Journal of Neuroscience* 13:1479–97, © Society for Neuroscience, 1993, with permission.

the goal location, their saccades ended up nearer the cued location than to any other potential goal location.

Proponents of the working-memory interpretation could argue that the monkeys do not make frank errors because the lesions, whether permanent or temporary, were unilateral. After all, we know that on the standard delayed response task unilateral lesions of the mid-lateral PF cortex cause only a mild impairment (Rosen et al. 1975), whereas the impairment after a bilateral lesion is severe (Goldman et al. 1971). So Funahashi et al. (1993a) made bilateral lesions in two monkeys, and did so in two stages. Figure 5.7 shows the data for one of these animals. This monkey had a greater impairment after the second lesion, but again most of the saccades ended near the target location (Figure 5.7). The lesions only rarely caused frank errors. At the longer delay of 6 seconds (not shown), the saccadic endpoints distributed more widely than with shorter delays, but the monkeys still made accuracy errors much more often than frank errors.

Having said that, we do not deny that monkeys with lesions or inactivations of the PF cortex do sometimes make frank errors. But an examination of what monkeys do after making frank errors shows that the impairment has little to do with retrospective working memory. Tsujimoto and Postle (2012) reported the effects of inactivating the mid-lateral PF cortex (area 46), so we take them up again in the next chapter. These inactivations caused frank errors on the oculomotor delayed response task. After monkeys made such errors, their immediate and next saccade targeted the appropriate goal (Figure 5.8). This finding shows that the monkeys had not forgotten the location of the cue or the location of the appropriate goal.

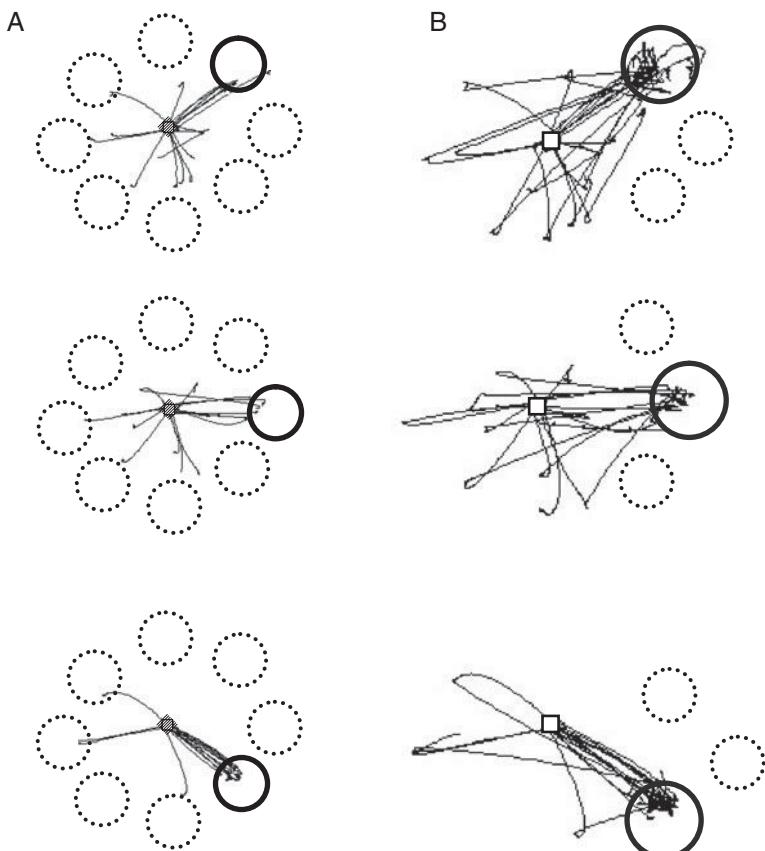


Fig. 5.8 Corrective saccades after a frank error. (A) After inactivating the mid-lateral PF cortex, the monkey made some saccades to incorrect goals. The correct goal for the top part of the figure was the upper right location, for the middle part it was the right location, and for the bottom part it was the lower right location. (B) An examination of the immediate aftermath of an incorrect saccade shows that the monkeys make a corrective saccade to the appropriate goal on that trial. Modified from Tsujimoto S, Postle BR. The prefrontal cortex and oculomotor delayed response: A reconsideration of the mnemonic scotoma. *Journal of Cognitive Neuroscience* 24:627–35, © 2012 by the Massachusetts Institute of Technology.

Tsujimoto and Postle also analysed the pattern of frank errors and found that the monkeys often chose the goal that had been appropriate and rewarded on the previous trial. Thus it is clear that the monkeys did not have a simple impairment in retrospective spatial working memory. Instead, as we propose in the next chapter, monkeys with PF cortex lesions have impairments in distinguishing between the previous goal and the current one.

So the evidence from disrupting delay-period activity does not support the view that the lesions cause the loss of retrospective sensory memories. Instead, it indicates that the lesions interfere with the accuracy of saccades made to unmarked locations and the ability to distinguish previous goals from current ones. Monkeys with lesions of the caudal PF seem to retain knowledge of the appropriate goal but have difficulty translating this knowledge into accurate saccades.

Eliminating the delay period

The lack of cues during the delay period has led to the assumption that the delay-period activity reflects the memory of the cue: retrospective spatial memory. If so, and if retrospective spatial memory is the key function of the caudal PF cortex, then we might expect diminished activity during tasks that have no delay period. More importantly, lesions of the caudal PF cortex should not cause an impairment on tasks that lack a memory requirement. Experimental results disagree with both ideas.

Gold and Shadlen (2007) presented monkeys with a cue composed of moving dots. The net motion of the dots, to the left or to the right, instructed a saccade to either a red or a green target, regardless of where the target appeared. There was no delay period; the monkeys made their choice as soon as they decided on the net direction of cue movement.

As explained by the accumulator–racetrack models that we introduce in Chapter 3, Gold and Shadlen found activity in the FEF that ramps up between the onset of the cue and the time of the saccade. They showed that this activity encodes the colour of the goal stimulus, red or green. So the FEF has task-related activity in a task that lacks either a delay period or a spatial memory requirement, and it appears to be as robust as in tasks that include a delay period.

Nevertheless, one could argue that ‘memory’ cells simply become inactive in such tasks, and that other kinds of cells become more prominent. So a stronger prediction is that a lesion should only cause an impairment if the task includes a delay period. But Keller et al. (2008) have presented evidence that this prediction does not hold. They taught monkeys a conditional visuomotor task in which the animals had to direct saccades to different locations depending on the colour of the central fixation point. Keller et al. then inactivated the FEF, either unilaterally or bilaterally. The inactivation led to an increase in errors, and these included not only inaccurate saccades but also frank errors. And bilateral lesions caused roughly twice the effect of unilateral ones. Here the task did not involve a requirement for retrospective spatial memory, and yet the lesion produced an impairment. These tasks did require the prospective coding of and attention to goals, however.

The tasks described so far involve saccades. But experiments with reaching movements lead to the same conclusion. Lawler and Cowey (1987) taught monkeys to reach to the left

after a black cue and to the right after a white one. They then made bilateral lesions in the caudal PF cortex, which caused a severe impairment. Petrides (1985) used a visual cue that told the monkeys whether to open a lit box or an unlit one. Again monkeys with lesions in the caudal PF cortex showed impairments. Neither experiment involved a delay period that required memory.

On all these tasks, the cue specified the goal for that trial, which could have been a location (Keller et al. 2008) or an object (Petrides 1985). And the goal could be the target of a saccade (Keller et al. 2008) or of a reaching movement (Lawler & Cowey 1987).

Lawler and Cowey (1987) suggested that after caudal PF cortex lesions the animals ‘neglected’ part of visual space, which means that they could not orient attention toward those places. But a similar lesion simply increases the time needed to search for a peripheral target rather than causing that search to fail (Wardak et al. 2004). So we suggest that monkeys with lesions of the caudal PF cortex can detect peripheral targets, if somewhat more slowly than normal. Their core impairment involves a difficulty in directing attention to the places and objects that serve as goals.

Summary

This section reviewed evidence from cell-recording and lesion studies that have been taken to support spatial working memory theory of the PF cortex (Goldman-Rakic 1998). We reject this conclusion here for the caudal PF cortex (area 8) and for the postero-lateral PF cortex (area 9/46) cortex on several grounds:

1. Most of the delay-period activity reflects covert attention to a potential goal rather than the maintenance of sensory cues in memory.
2. Lesions of the caudal or post-lateral PF cortex rarely cause frank errors in which the monkey makes a saccade to an incorrect location rather than the cued one. Instead, these lesions mainly cause inaccurate saccades, which end nearer the correct location than to any other potential target. When frank errors do occur, lesioned monkeys immediately correct their error and thereby show that they remember the cued location.
3. These areas encode goals in tasks that lack a delay period.
4. Lesioned monkeys have impairments on tasks that lack a delay period, and thus the function of these areas does not depend on bridging a time gap.

The evidence therefore suggests that the caudal and postero-lateral PF cortex functions in the search for and attention to goals rather than in working memory. We take up other grounds for rejecting the working memory theory in Chapter 6, where we discuss the dorsal PF cortex. In Chapter 10, we address the working memory theory for the PF cortex as a whole.

Attention based on learning

In the experiments discussed in the previous section, the monkeys had to learn which goal to attend to by using reward feedback to influence its future choices among goals.

This feature of the tasks has not always received the consideration it deserves. An important aspect of caudal PF cortex function involves the distinction between goal-oriented and stimulus-driven attention.

Goal-oriented versus stimulus-driven attention

The distinction between goal-oriented and stimulus-driven attention relates to learning. As always in this book, by goal we mean the objects and places that serve as the targets for actions. Stimulus-driven attention depends on the salience of the target, for example, its brightness or suddenness of onset, which *captures* attention. This bottom-up form of attention relies on innate mechanisms, not learning. In goal-oriented attention, the subject of an experiment must *learn* which stimulus to attend to, whether as in the case of monkeys by reward feedback or in the case of human subjects by either instruction or feedback.

It is important to note that the distinction between stimulus-driven and goal-oriented attention does not correspond to one between pop-out search and conjunction search. In both cases, the monkey learns the target through feedback or the person learns the target through instruction or feedback. The two kinds of search differ in that in pop-out search the target stands out from a set of identical distractors, whereas in conjunction search the target shares features with the distractors but differs in having a particular combination of those features. The distractors need not be identical to each other. Both types of search require learning, and so inactivation of the FEF impairs performance on both (Wardak et al. 2004). Furthermore, when Wardak et al. (2010) performed an imaging experiment on monkeys during a pop-out search task, the predominant activation occurred in the caudal PF cortex, including the FEF, with only a small activation in the posterior parietal cortex.

Goal-oriented attention involves the PF cortex because, as Chapter 4 reviews, it receives certain kinds of information about outcomes more directly than other areas. Specifically, the orbital PF cortex can provide valuations of potential goals both in specific terms and in terms of a ‘common currency’. And this information can be conveyed from orbital PF to other PF areas, which connect to caudal PF cortex. The interactions between the orbital and caudal PF cortex lead to the search for valuable objects and attention to them.

The enhancement effect

When the caudal PF cortex orients attention to a goal, one result is called the enhancement effect; cells have larger responses to stimuli at attended locations compared to unattended ones. Both overt and covert attention cause this effect.

Goldberg and Wurtz (1972) discovered the enhancement effect for neurons in the superior colliculus. Many of these neurons show an enhancement of activity for saccade targets. In a follow-up study by Goldberg and Bushnell (1981), cells in the posterior parietal cortex showed enhancement not only before saccades (overt attention), but also during covert attention. Likewise, imaging shows enhanced activation of attended stimuli (Corbetta et al. 2000), and the enhancement of activation occurs in the region of the retinotopic map that corresponds to the attended location (Breczynski & DeYoe 1999).

In an early study of cell activity in the FEF, Goldberg and Bruce (1985) found the enhancement effect for saccade targets (overt attention), but not for covert attention. In a later study, however, Kodaka et al. (1997) reported that many cells showed enhancement of the visual response on an attention task that required the monkeys to release a lever when a peripheral stimulus dimmed. So it seems that, as in the posterior parietal cortex, cells in the FEF show enhanced sensory responses to both overtly and covertly attended locations.

Hasegawa et al. (2000) recorded from area 8Ad and presented an object-like goal in an array of distractors. Within 135 milliseconds of target presentation, these caudal PF cortex cells showed an enhancement in their response if the goal appeared in the cell's receptive field. Enhancement did not occur if the target appeared outside the cell's receptive field or if stimuli other than the goal appeared in the receptive field. This finding agrees with the idea that the caudal PF cortex contributes to or reflects the search for learned goals.

Top-down effects

Given that the enhancement effect occurs both in the PF cortex and in more caudal areas such as the posterior parietal cortex, we need to know what drives the enhancement. From the enhancement effect, alone, we cannot distinguish cause and effect. We cannot simply assume that the cells respond more because of the effect of top-down attention. Nevertheless, the properties of accumulator-racetrack networks show how this mechanism could work (Chapter 3). If a PF cortex network represents the goal for a future action, then it could cause sensory representations of that goal, elsewhere in the cortex, to reach their threshold faster. The result would be top-down biased competition (Desimone & Duncan 1995) based on learned goals. The result would amount to 'looking for' or maintaining attention on the goal.

A top-down bias could explain how enhancement can occur in lower order areas. We have already mentioned that Armstrong and Moore (2007) applied intracortical microstimulation to the FEF and showed that it enhances the response of cells in visual area V4. And it does so for a particular part of visual space. This finding suggests that when a monkey attends to that part of space, the FEF exerts a top-down bias on V4 that favours the representation of that location.

Chapter 3 elaborates the idea that the PF cortex can bias the competition among lower order behavioural-control systems, and Desimone and Duncan (1995) have proposed a biased competition model of top-down effects on lower-order visual areas.

Desimone and Duncan did not present evidence that top-down effects originate in the PF cortex, as opposed to other areas. However, we know that cells in the caudal PF cortex show activity that differs according to the nature of the current task. When the location of a cue has little relevance to the choice of action, only a minority of cells encode that location (Chen et al. 2001). When a cue's colour and shape have a high relevance, a large number of caudal PF cells come to encode those features (Bichot et al. 1996).

Corresponding changes occur in sensory areas. When the task requires the monkey to attend to motion, neurons in areas MT and MST show enhanced responses to that feature

of the stimulus (Treue & Maunsell 1996). When the task requires that the monkey attend to orientation, cells in area V4 show enhanced response to that feature (McAdams & Maunsell 1999).

However, the enhancement effect depends on the fact that the monkeys have *learned* which dimension, motion, or shape, is relevant for the task. The animal only receives rewarding feedback if it attends to the relevant dimension.

The caudal PF cortex has extensive connections with the more rostral parts of the PF cortex, and cell activity in many parts of the PF cortex reflects the currently relevant stimulus dimension. For example, Lauwereyns et al. (2001) taught monkeys a go no-go task in which the relevant stimulus dimension alternated between colour and motion. They found that 44% of their cells preferred the colour-relevant condition and 24% preferred the motion-relevant condition. The former tended to be in the ventral PF cortex and the latter in the dorsal PF cortex. The rostrally located cells in both areas tended to reflect the relevant dimension more often than cells in the caudal PF cortex, where cells more often encoded the appropriate response: go or no-go.

Lauwereyns et al. called these caudally located neurons ‘integration cells’ and suggested that they provided part of the output from the PF cortex to other cortical areas. So more rostral parts of the granular PF cortex can influence the caudal PF cortex and thereby affect sensory information processing in other parts of the cortex. They could also do so directly.

If the enhancement occurs as the result of a top-down effect, it should be possible to show that it occurs earlier in the PF cortex than in the caudal sensory areas. So Zhou and Desimone (2011) recorded simultaneously from the FEF and area V4 while monkeys performed a visual search task. When the monkeys attended to particular features of a stimulus, enhanced sensory responses occurred in both areas, but the latencies of these effects suggested the FEF that provided a top-down bias to V4. In this way, the caudal PF cortex could modulate processing of stimulus features in sensory cortex.

The mechanism of top-down attention might involve the development of synchrony between slow-wave oscillations in the two areas. Like the signal measured by imaging experiments (Chapter 1), slow changes in electrical potentials probably reflect synaptic activity rather than neuronal discharge rates. As in the experiment by Zhou and Desimone, Gregoriou et al. (2009) recorded from the FEF and V4, and they did so while the monkey attended to a stimulus in a cell’s receptive field. They observed the development of the coupling between the oscillations of these two areas, which the FEF appeared to initiate. The synchronization occurred most prominently in the gamma band, which has been proposed as a general mechanism for the interaction among cortical areas (Womelsdorf et al. 2007).

The finding that the enhancement occurs earlier in the PF cortex than in visual areas does not demonstrate that the PF cortex causes enhancement in those areas. So Rossi et al. (2009) studied the effects of a PF lesion. They taught monkeys to discriminate the orientation of bars in a grating. The colour of a central cue told the monkey to judge the orientation in a grating that had the same colour. The monkey saw three gratings, and only one had the relevant colour, which could change either from trial-to-trial or remain

the same for a block of trials. Unilateral lesions of the dorsal and ventral PF cortex, combined with transection of the corpus callosum, allowed Rossi et al. to compare performance when the lesioned or intact hemisphere processed the stimuli. For the lesioned hemisphere, the monkeys showed severely elevated thresholds for discriminating orientation, and frequent changes in the relevant colour exacerbated this deficit.

Rossi et al. did not show that the PF lesion abolished the enhancement effect in visual areas, but some cortical stimulation experiments provide evidence that it might. Morishima et al. (2009) used single-pulse transcranial magnetic stimulation (TMS) over the FEF of human subjects. Their subjects saw faces composed of moving dots and had to make judgements either about the motion of the dots or about the gender of the face. Thus, they had to attend either to motion or to faces. Morishima et al. used EEG to record activation from area MT and from the fusiform face area of the temporal cortex, as they stimulated the FEF. When the subjects prepared to make a judgement about motion, the stimulation influenced activation in area MT, whereas when they prepared to make judgements about gender, it influenced activation in the fusiform face area. Thus, stimulating part of the granular PF cortex generated a top-down bias toward the relevant stimulus dimension in posterior visual areas.

Summary

The caudal PF cortex functions in goal-oriented attention, which involves searching for and attending to goals based on prior learning. According to our proposal, the orbital PF cortex learns to assign outcomes to the choices among stimuli, including specific outcomes such as the sight, taste, and smell of foods and fluids. As Chapter 4 proposes, the granular parts of the orbital PF cortex represent both these specific outcomes and outcomes in a ‘common currency’. And these orbital areas update the value of these representations in accordance with an animal’s current needs.

Through indirect interconnections between the orbital and the caudal PF cortex, the latter searches for and evaluates stimuli and orients both overt and covert attention to the most valuable ones. The mechanism by which it does so involves the enhancement of activity in sensory areas of cortex, probably as a result of a top-down bias from the PF cortex. Other parts of the PF cortex can provide that top-down bias either indirectly via the caudal PF cortex or directly through connections with the sensory areas of cortex.

Conclusions

How the caudal PF cortex can do what it does

This chapter shows how the connections of the caudal PF cortex explain what it contributes to the PF cortex as a whole. Three of these connections seem most important:

1. Connections with the orbital PF cortex provide the caudal PF cortex with the learned and updated value of viewed items, indirectly through areas 12 and 46 (Barbas & Pandya 1989).
2. Through connections with both the dorsal and ventral visual streams, the caudal PF cortex searches for and directs attention to places and objects of value. These connections include projections to parietal and temporal areas, which are thought to cause

the enhancement of sensory responses to places and objects, thus providing a top-down bias among competing sensory representations.

3. Projections to oculomotor nuclei, both directly and indirectly via the superior colliculus and basal ganglia, allow the FEF to direct overt attention through eye movements.

These connections enable the caudal PF cortex to search for goals of value in a cluttered environment and to direct attention toward them. It does so specifically for learned goals—goal-oriented attention—as opposed to reflexive or stimulus-driven attention.

Proposal

We can now propose a specific function for the caudal PF cortex, in brief and slightly elaborated form:

In brief:

The caudal PF cortex searches for and orients attention toward valuable goals, based predominantly on vision.

Expanded:

The caudal PF cortex, along with the postero-lateral PF cortex, searches for and orients attention toward goals of learned value, based predominantly on vision, as assessed in terms of current biological needs. It does so either by covert attention or overt attention (eye movements).

Why other areas cannot do what the caudal PF cortex does

Because of its connections, only the caudal PF cortex can perform these functions. As Chapter 4 shows, the orbital PF cortex first receives detailed information about the sight, smell, taste, and ‘mouth feel’ of foods. Through its indirect connections with the orbital PF cortex, the caudal PF cortex can receive information about the desirability of specific goals based on current biological needs.

The posterior parietal cortex, on the other hand, does not receive much information about specific foods or fluids. It has few, if any, inputs that convey specific outcomes, from the orbital PF cortex or from any other cortical area. Furthermore, it has sparse, if any, connections with the amygdala. The temporal cortex does receive inputs from the amygdala, but it cannot easily combine those signals with the olfactory, gustatory, and visceral features of outcomes as the PF cortex can. Both the caudal PF cortex and the posterior parietal cortex play a role in attention. But as we have stressed, the caudal PF cortex functions in attention to goals that monkeys have learned to be of value, probably because it and not the posterior parietal cortex receives prefrontally mediated information about specific outcomes.

Contribution to foraging choices

In the laboratory, primates often reach to or look at goals in the form of coloured shapes or spots of light. In their natural surroundings, their goals include foods, signs of food,

and places of learned value. As Chapter 2 explains, the PF cortex that evolved in early primates had two new granular areas: the caudal PF cortex and the granular parts of the OFC.

We propose that these two granular areas worked together in early primates, as they continue to do in modern primates. But to understand how they contributed to foraging choices in early primates, we need to understand how these extinct ‘visual animals’ saw the world.

It is a conceit of our species to see the vision of other animals through our own eyes. But early primates did not have eyes like ours, in large measure because they lacked a fovea, which evolved later (Chapter 2). Overt attention, by definition, depends on the fovea, and so when early primates attended and searched for objects, they used covert attention to do so. We propose that the orbital PF cortex of early primates provided the learned value of visible objects in terms of current needs (Chapter 4). When combined with the search and attention functions provided by the caudal PF cortex, early primates could choose among objects and places, find them in a cluttered environment, and attend to them (covertly).

Later in primate evolution, a fovea and trichromatic vision evolved and new PF areas appeared (Chapter 2). The next two chapters, on the dorsal PF cortex and the ventral PF cortex, respectively, explore what advantages these areas bring to anthropoid primates.

Chapter 6

Dorsal prefrontal cortex: generating goals based on recent events

Overview

The dorsal PF cortex contributes to the generation of goals based on order, timing, and spatial contexts, and its connections explain why it alone can do so. The dorsal PF cortex, which includes the mid-lateral PF cortex (area 46), functions through connections with the posterior parietal cortex, the premotor cortex, and other parts of the PF cortex. Parietal connections provide many of the spatial and temporal contexts used to generate goals. Connections with the premotor areas lead to the achievement of these goals, usually by hand movements. Connections with the orbital PF cortex allow the dorsal PF cortex to predict the specific outcome of their goal choices based on a single event. The dorsal PF cortex lies at the end of the dorsal visual stream, and so it can plan sequences of goals and it can specify these goals in either concrete or abstract terms. After generating goals, the dorsal PF cortex can prospectively encode them until the time comes to act. Given that the dorsal PF cortex evolved in anthropoid primates (Chapter 2), we propose that it provides an advantage in using the order, timing, and location of recent visual events to guide foraging choices and to generate sequences of goals that are optimized for efficiency.

Introduction

Chapter 2 explains that the primate PF cortex expanded in anthropoids as new areas appeared. Chapter 3 touches on a few of them, the polar PF cortex (area 10), for example, but in this chapter and the next they are the main topic. Because anthropoids depend on lengthy foraging excursions during daytime, they use considerable amounts of energy and face a high risk of predation. This kind of life placed a premium on making good foraging choices. Among the factors influencing such choices, the locations, timing, and order of visual events figure prominently, as anthropoids exploit their advances in foveal and colour vision. As Chapter 2 explains, these advances included the exquisite visual acuity provided by the fovea and the enhanced discriminative capacity afforded by trichromatic vision.

This chapter explains that foraging choices depend, in part, on a current context, which is specified by stimuli that are available at the time of the choice, as well as the memory of recent visual events. To understand what we mean by this, consider a simple laboratory task: delayed matching-to-sample. The monkey sees one stimulus as a sample and later sees one or more stimuli that require a choice. That choice depends not only on the stimuli present at the time of the choice, but also on a memory based on the sample stimulus. Together these two factors compose the current context for choosing a goal.

Because memories contribute to the current context, the subjects in experiments of this kind face a problem: several events will have occurred recently and several goals will have been chosen. The largest part of this chapter explores how the dorsal PF cortex helps anthropoid primates solve this problem. Much of the literature relies on one task and one area: the delayed response task, which depends on the mid-lateral PF cortex (area 46). Accordingly, we focus our discussion on this task, which Chapters 1 and 5 also mention. We argue that because subjects experience a series of visual events in this task and achieve a series of goals, they need to pick out the event that determines the current goal. We then review a series of other tasks that also require the subject to generate goals on the basis of a current context.

Areas

In macaque monkeys, the mid-lateral PF cortex lies in the rostral two-thirds of the principal sulcus (Figure 6.1). However, it also extends onto the convexity cortex dorsal and ventral to this sulcus. The mid-lateral PF cortex (area 46) goes by many names, some well defined, others less so.

Walker (1940) called the cortex along the entire length of the principal sulcus area 46, but more recently Petrides and Pandya (1999) distinguished area 9/46 around the caudal end of this sulcus (see Figure 1.2). To avoid confusion over these various uses of the term

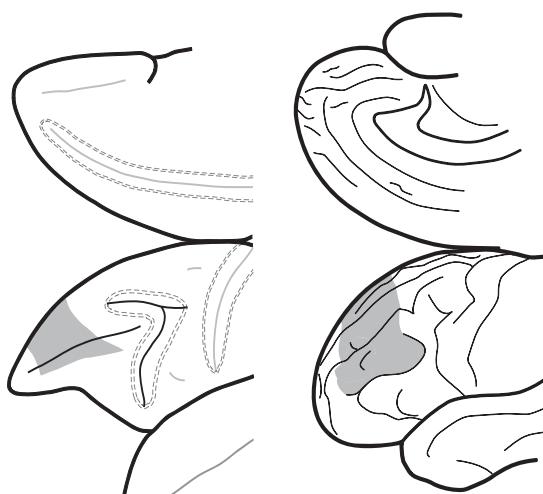


Fig. 6.1 The dorsal PF cortex in macaque monkeys (left) and humans (right). Format as in Figure 1.2.

area 46, we call the rostral two-thirds of Walker's area 46 the *mid-lateral PF cortex* and the caudal third of it the *postero-lateral PF cortex*. In humans, these divisions lie within the middle frontal gyrus, between the superior and inferior frontal sulci.

Despite these new terms, there remains plenty of room for confusion. The term dorso-lateral PF cortex originally referred to the whole lateral PF cortex in monkeys (Pribram et al. 1952) but later came to mean only the cortex in and dorsal to the principal sulcus (Mishkin et al. 1969). In the imaging literature, it has become common to refer to the dorsolateral PF cortex, but the term is often used very loosely, with little attention to anatomical landmarks. As a result, we avoid that term in this book. Table 1.2 presents the terminology that we have adopted instead. We take the dorsal PF cortex to include the cortex in both banks of principal sulcus and the convexity cortex dorsal to it (area 9), but not the medial parts of area 9. These divisions are not the final word, of course, but they reflect connections to a reasonable extent.

Connections

Figure 6.2 illustrates some of the corticocortical connections of the dorsal PF cortex. As Chapter 1 explains, these connections compose an anatomical fingerprint.

1. The mid-lateral PF cortex (area 46) has strong connections with the posterior parietal cortex, especially caudal parietal areas (Petrides & Pandya 1984, 1999, 2009). As the previous chapter mentions, many of the neurons in the posterior parietal cortex encode visuospatial information. However, parietal cells also encode time intervals (Leon & Shadlen 2003) and activations occur in the left intraparietal sulcus when human subjects make judgements about recency (Dudukovic & Wagner 2007).
2. The mid-lateral PF cortex, together with lateral area 9, connects with the multimodal area called area TPO, also known as the superior temporal polysensory area (STP), which lies in the upper bank of the superior temporal sulcus (Seltzer et al. 1996; Petrides & Pandya 1999). Cells in this area respond to somatosensory, auditory, and visual stimuli (Bruce et al. 1981).
3. The mid-lateral PF cortex also receives an input from the perirhinal cortex (Petrides & Pandya 1999), which functions in the identification of objects (Murray et al. 2007). This connection suggests that the mid-lateral PF cortex receives a direct input concerning objects and not just an indirect one from the ventral PF cortex (Chapters 7 and 8).
4. The mid-lateral PF cortex receives an input from the secondary somatosensory area (S2) (Petrides & Pandya 2002b) and area PFG in the rostral part of the inferior parietal cortex (Rozzi et al. 2006). Cells in these areas respond to somatosensory stimulation (Hyvarinen 1981), as do cells in the mid-lateral PF cortex (Taniila et al. 1993). This feature distinguishes the mid-lateral PF cortex from the caudal and postero-lateral PF cortex, where cells have mainly visual and attentional properties (Chapter 5).
5. The mid-lateral PF cortex connects with the dorsal and ventral premotor cortex (Wang et al. 2002) as well as with the pre-supplementary motor area (preSMA) (Wang et al. 2005) and the rostral cingulate motor area (CMAr), which lies in the

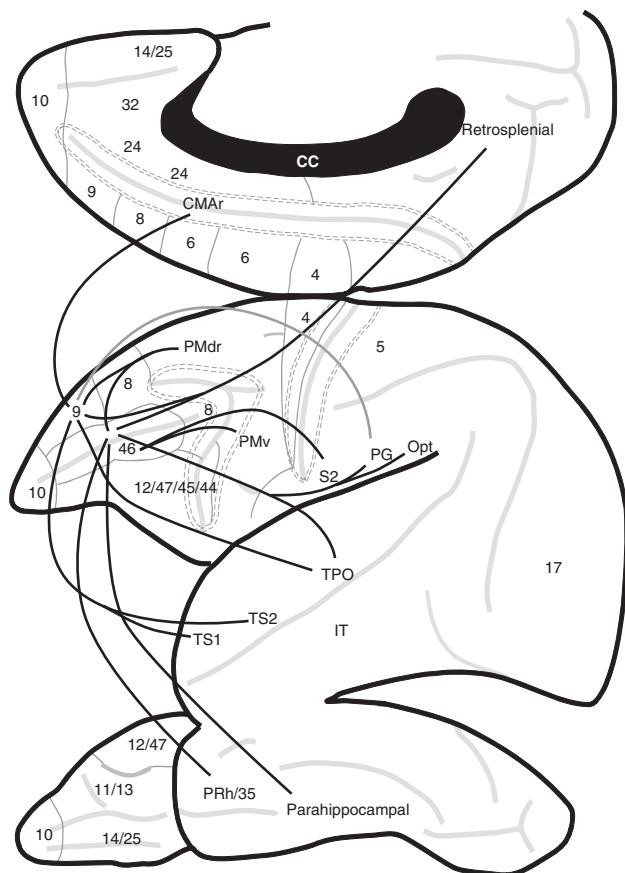


Fig. 6.2 Selected connections of the dorsal PF cortex. Figures 1.4 and 1.5 give the names of sulci and areas. Lines connect some of the areas that have direct axonal connections with the dorsal PF cortex, assumed to be reciprocal unless otherwise stated.

cingulate sulcus (Dum & Strick 1993). These projections primarily involve premotor areas that represent the hand and arm rather than the foot and leg. A specialization for forelimb representations has been shown for the rostral part of the dorsal premotor cortex (Tachibana et al. 2004), the ventral premotor cortex (He et al. 1993), the preSMA (Luppino et al. 1991), and the CMAr (He et al. 1995). Thus, the mid-lateral PF cortex has a preferential role in reaching, manipulation, and feeding movements, as opposed to the movements of locomotion (Chapter 2).

6. The mid-lateral PF cortex has strong connections with the anterior cingulate cortex (Petrides & Pandya 1999). Chapter 3 explains that the anterior cingulate cortex plays a role in the valuation of actions and in switching among actions based on those valuations (Walton et al. 2007).
7. The mid-lateral PF cortex connects with the retrosplenial cortex (Morris et al. 1999). In turn, projections from the retrosplenial cortex go to the parahippocampal

gyrus and to the presubiculum (Kobayashi & Amaral 2007). We suggest that these connections could play a role in the retrieval of memories concerning events and that such retrieval depends on a temporal or spatial context (Vann et al. 2009).

8. The connections of the lateral part of area 9 have received relatively little attention, in part because so little functional data have drawn interest to it. This part of the dorsal PF cortex has connections with the rostral part of the dorsal premotor cortex (Petrides & Pandya 1999) and the CMAr (Morecraft & van Hoesen 1993). Like the medial part of area 9, it also has connections with the superior temporal cortex, which might convey auditory information (Petrides & Pandya 1984; Saleem et al. 2008). Finally, the lateral part of area 9 has connections with the inferior part of the posterior parietal cortex (area PG) (Cavada & Goldman-Rakic 1989) and the retrosplenial cortex (Kobayashi & Amaral 2003).

Summary

The mid-lateral PF cortex has strong connections with the posterior parietal cortex, the premotor cortex, and, indirectly, with the hippocampal system. It is also interconnected with other parts of the PF cortex, such as the orbital PF cortex. No other cortical area has this pattern of connection. As a result, it is well positioned to integrate the information processed by the orbital PF cortex, the dorsal visual stream, and the hippocampus, as well as to provide information to the premotor cortex.

Delayed response task

The mid-lateral PF cortex resembles the caudal PF cortex in receiving visuospatial information from the posterior parietal cortex. Thus, it is not surprising that monkeys with lesions of either area cause some disruption of performance on the oculomotor delayed response task and on the classical version of the delayed response task. On both tasks, spatial cues guide goal choices and the monkey must choose among possible spatial goals. Of course, by definition the oculomotor delayed response task requires a saccade to the goal, whereas the classical delayed response task requires a reaching movement. Chapter 5 explains that lesions of the caudal PF cortex and the postero-lateral PF cortex cause accuracy errors on the oculomotor delayed response task, which makes sense in the light of their connections with the dorsal visual stream. These lesions do not cause many frank errors and, when they do, the monkey corrects these errors promptly (Tsujimoto & Postle 2012).

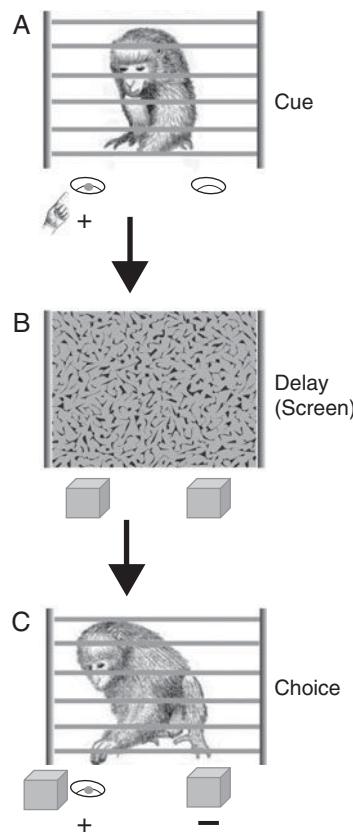
By contrast, permanent lesions of the mid-lateral PF cortex (area 46) cause a devastating impairment on the classical delayed response task. When monkeys learn the delayed response task prior to surgery, they perform the task at no better than chance levels after lesions of the mid-lateral PF cortex (Goldman & Galkin 1978). That is, lesioned monkeys make as many frank errors as correct choices. When they attempt to learn the task for the first time after sustaining lesions of the mid-lateral PF cortex, they cannot do so, even with brief (1 second) delay periods (Battig et al. 1960). And they never recover, at least not within a time frame that anyone has tested.

One important methodological difference could account for part of this discrepancy. In the classical delayed response task, the monkey reaches toward and displaces the lid that lies over a food-well. This means that on this version of the task, unlike the oculomotor delayed response task, the subject can only make frank errors. Accuracy errors, if they occur, would not be recorded.

Another difference might also be important. Monkeys can solve the oculomotor delayed response task by covertly attending to the goal location during the delay period. But the way in which experimenters conduct the classical delayed response task makes covert attention to the goal very difficult. Traditional testing methods involve the Wisconsin general test apparatus (WGTA). In this device, an opaque screen descends during the delay period so that the monkey cannot see the relevant location during the delay (Figure 6.3). In the oculomotor version of the task, the monkey can see the goal location in peripheral vision, although it is no longer marked at the time of the saccade.

In principle, monkeys performing the classical delayed response task could still covertly attend to the goal's side of the WGTA or could orient posturally to that side in some way. However, lowering the screen often causes the monkey to move within the testing chamber. Passingham (1971) monitored the position of normal monkeys during the

Fig. 6.3 Testing procedure for the delayed response task in a Wisconsin general testing apparatus (WGTA). (A) An experimenter baits one of two food wells (+) as a monkey observes from its testing cage. This action serves as the visual cue event. (B) The experimenter then lowers an opaque screen for the delay period. Identical objects cover the food well. (C) After the experimenter lifts the screen, the monkey chooses between the two food wells, displaces one of the objects, and either obtains a reward if correct (+) or does not if incorrect (-). Modified from Murray EA. Contributions of the amygdalar complex to behavior in macaque monkeys. *Progress in Brain Research* 87:167–80 © 1991, with permission from Elsevier.



delay period and found that even when they had solved the problem they crossed from one side of the chamber to the other on 40% of the trials. So macaque monkeys do not need to orient bodily in order to solve the problem posed by the delayed response task, and it seems likely that the testing methods probably preclude the use of covert attention to do so. Accordingly, the relative lack of frank errors on oculomotor delayed response could reflect the continued capacity to covertly attend to the location of the goal, and the severe impairment on the classical version of the delayed response task could result from disrupting this strategy.

The delayed response task can, of course, be presented without the opaque screen. During the delay period, the food-wells can lie beyond the subject's reach. Under these conditions, it seems more likely that monkeys could adopt some kind of postural or attentional approach to bridging the delay period or use other strategies to do so. Wilson et al. (1963) found that normal monkeys sat on the correct side of the testing chamber at the beginning of the delay period and remained on that side at the end of the delay. They then reached the shortest distance to the goal when given the opportunity to do so. Monkeys with PF cortex lesions also sat on the correct side at the beginning of the delay, but they reached to the opposite (wrong) goal at the end of the delay as often as they reached the shorter distance to the correct goal. This finding shows that postural or attentional bridging of the delay period is not sufficient for monkeys with PF lesions to perform the delayed response task correctly.

It is not clear why monkeys do not adopt the strategy of remaining on the correct side of the WGTA throughout the delay period. This strategy would solve the problem. Perhaps they do not appreciate that what they see at the beginning of the delay period indicates where they should reach at the end of the delay. In other words, lesioned monkeys might not recognize that the visual events before the delay interval have any relevance to their forthcoming choice. Normal monkeys do recognize this relationship and do not need to adopt either a postural orientation strategy or an attentional strategy to perform the task.

In a later section, we develop the idea that to solve the problem posed by the delayed response task, the monkey needs to know that the visual events before the delay period provide the key to their choice of a goal afterward. We propose that monkeys with lesions of the mid-lateral PF cortex either cannot learn this rule or fail to remember and apply it.

Importance of the delay period

Chapter 5 mentions that although monkeys with lesions of the caudal PF cortex have only slight impairments on the oculomotor delayed response task, they are also impaired on conditional visuomotor tasks that have no delay period. By contrast, monkeys with lesions in the mid-lateral PF cortex *only* have impairments in tasks that include a delay period.

Passingham (1985a) devised a conditional visuomotor task with no delay. Two panels in the centre of a display, one above the other, provided the cues. The monkeys learned that if a light appeared in the top panel then it should choose a target to one side; if a light

appeared in the bottom panel then it should choose a target on the other side. So the task involved a spatial cue and a spatial goal like the delayed response task, but unlike the delayed response task it did not include a delay period. Monkeys with lesions of the mid-lateral and postero-lateral PF cortex could learn this task normally.

Results from Stamm (1969) also show that the delay is a critical factor in producing the impairment. He inactivated either the mid-lateral or the postero-lateral PF cortex at different time points during a trial. In the early part of the delay period, disruptive stimulation of the mid-lateral PF cortex (area 46) caused performance to fall to chance level on the delayed response task. Stimulation of the postero-lateral cortex had a lesser effect. This finding is consistent with the results of a study by Butters and Pandya (1969) in which they showed that lesions in the central third of the principal sulcus led to a very severe impairment on the delayed alternation task, whereas lesions in the posterior third had a much smaller effect.

Taken together, these results support two conclusions. First, the impairment on the delayed response task does indeed result from the imposition of a delay period. Second, the mid-lateral PF cortex plays a necessary role in this task. It also does so in the closely related delayed alternation task.

Delay-period activity

The most commonly cited account of the delayed-response impairment holds that the monkeys fail to remember the location of the cue, and thus the deficit can be described as one of retrospective spatial working memory. The fact that one can record activity during the delay period, and that this activity seems, at first glance, to encode a memory of the cue's location has been construed as evidence in support of this conclusion. However, such activity occurs in many parts of the PF cortex, and in other areas besides. And Chapter 5 explains that delay-period activity does not always encode spatial memories. When investigators study cell activity in sufficient comparison conditions, they can see that much of the so-called memory activity actually encodes attended locations. Nevertheless, some of the delay-period activity does encode remembered locations, and so it remains possible that delay-period activity in the mid-lateral PF cortex mediates retrospective working memory.

Kojima and Goldman-Rakic (1984) recorded from the mid-lateral PF cortex (area 46) in an attempt to verify the spatial working memory theory. They used two conditions. In one, the cue disappeared during the delay period and in the other the cue remained visible throughout the trial. Of 62 cells that encoded location during the delay period, 44 either showed equal or greater delay-period activity when the stimulus remained visible. Only 12 cells had more activity when the stimulus had disappeared. Tsujimoto and Sawaguchi (2004b) used the oculomotor delayed response task with similar conditions, and confirmed this pattern of results.

Four possible explanations for this finding seem most likely:

1. Even when the cue remains visible, nothing prevents the monkeys from 'remembering' its location. So they might 'remember' the cued location in both conditions.

2. The monkeys might fixate the goal in both conditions. Kojima and Goldman-Rakic (1984) did not record eye position, so we cannot rule out overt attention as an account for their result.
3. The monkeys might covertly attend to the goal in both conditions.
4. The monkeys might encode the location of a spatial goal in both conditions. This representation might include a planned action or it might specify the goal independent of the action needed to achieve it.

Of these four explanations, only the first is consistent with the interpretation of Kojima and Goldman-Rakic (1984). They concluded that delay-period activity reflects the representation of the cue's location in retrospective memory, in line with the spatial working memory theory. However, it seems unlikely that the monkey would 'remember' a stimulus that they could see. The second account, in terms of overt attention, could explain the results of Kojima and Goldman-Rakic but not those of Tsujimoto and Sawaguchi. In the latter study, the monkeys had to fixate a central location throughout the delay. The third account, in terms of covert attention, could also explain the results of both studies, but it is not compatible with the account in terms of retrospective working memory.

This leaves the fourth account, which interprets the delay-period activity as reflecting the location of the spatial goal, as first suggested by Fuster (1973). In other words, it suggests that delay-period reflects prospective, as opposed to retrospective, memory. The monkey performs many trials each day, which means the cue and goal locations from previous trials interfere with each other in memory. The monkey can overcome this interference by encoding the goal location as soon as it sees a cue on any particular trial.

Chapter 5 reviews some evidence that seems to argue against the prospective encoding of goals. Most cells encode the cue location in an antisaccade task, with only a minority encoding the goal location. In another study, cells encoded cued locations even when they did not serve as future goals. However none of these studies focused clearly on cells in the mid-lateral PF cortex, as opposed to the postero-lateral or caudal PF cortex.

In a study that we take up in more detail later in this chapter, Genovesio et al. (2006a) did study cells in the mid-lateral PF cortex, among other neuronal populations, and their experimental design allowed them to distinguish between the retrospective and prospective coding of locations. They showed that cells in the mid-lateral PF cortex encode the current goal location as soon as it is possible to do so and that retrospective coding dissipates at this time. We also present data in a later section showing that prospective activity of this kind can protect against interference in memory (Sakai et al. 2002a).

Summary

Monkeys with mid-lateral PF cortex lesions perform the delayed response task at chance level, and they do not recover. Disruptive electrical stimulation during the delay period causes an impairment, and in tasks that do not have a delay period monkeys perform

normally. Delay-period activity occurs in the mid-lateral PF cortex, and it encodes a location. This activity has been interpreted in terms of retrospective spatial memory, but the evidence shows that such activity also encodes the location of the current goal (prospective coding) and attended locations.

The role of interference

On the delayed response and delayed alternation tasks, a series of trials unfolds each day, and this creates severe interference in memory. On the delayed response task, monkeys receive cues from two or more locations as the trials add up; and on both the delayed response and delayed alternation tasks monkeys choose among the same locations over a series of trials.

Evidence for the effect of interference

An experiment by Diamond and Goldman-Rakic (1989) suggests that interference may be an important factor in causing the delayed response impairment. They tested monkeys with dorsal PF lesions on a modified delayed response task and analysed the errors that monkeys made after they had twice chosen the same side correctly. When the correct location on the current trial, by chance, matched the correct location on the previous two trials, the monkeys achieved a score of 85% correct. When the correct location on the current trial did not match the previous two trials, the monkeys performed at chance level (50% correct).

One might try to interpret this finding by suggesting that the monkeys perseverated. But perseveration would lead to below-chance performance, and instead the monkeys performed at chance level (50% correct). The fact that the lesioned monkeys performed at chance level suggests that they recognized that the cue had changed from the previous two trials. However, they did not know which location to choose, so they based their choice on the fact that both possible choices had produced rewards at roughly equal frequency, as averaged over recent trials.

Normal monkeys can learn to base their choice instead on a single event. On the classical delayed response task, this event consists of seeing a peanut being placed in one of the food-wells. In other versions of the delayed response task, the relevant event consists of a visual cue flashing somewhere in space.

In Chapter 4, we point out that monkeys with orbital PF lesions do not perseverate, but instead base their choices among objects on the past history of events, averaged over many trials. Intact monkeys, by contrast, can assign an outcome to the single, specific choice that seems to have caused it. We suggest something similar for the mid-lateral PF cortex. In the delayed response task, the visual event prior to the delay period leads to the generation of the appropriate goal, based on that single event. Without this influence, choices depend on an average of many previous events.

The delayed response task used by Diamond and Goldman-Rakic is a modification of a task devised by Piaget (1954) to assess the ability of human infants to understand object permanence. It is called the ‘A-not-B’ task. The experimenters hide a toy at location A, and the infant retrieves it. They then hide the toy at location B. Even though the infants see this visual event, they tend to reach back to location A (Harris 1989).

The A-not-B task usually requires the infants to reach for targets that they cannot see. Remarkably, they sometimes reach to A even when they *can* see the object at location B under a transparent cover (Butterworth 1977). Thus the infants seem to remember that they chose location A to get the toy in the recent past, and so they do that again rather than basing their choice on the most recent visual events. In other words, they seem to repeat a recently reinforced choice rather than make a choice based on the visual event of the toy being hidden at location B. When more mature, children easily learn to use the most recent event, the hiding of the toy at location B, to choose that location as their goal.

When viewed in the same way, the impairment on the delayed response task can be said to involve a difficulty in resolving trial-to-trial interference rather than a failure of retrospective memory. From this perspective, trial-to-trial interference results from the previous choice of location A in the A-not-B task or the previous choices of the alternative location in the delayed response task.

In support of this idea, there is imaging evidence that points to a role for the mid-lateral PF cortex when there is interference in memory. Owen et al. (1999) gave two spatial tasks to human subjects. In one, they presented five locations and tested memory for the items immediately afterwards. The other task was the *n*-back task. In the two-back task, the experimenters present stimulus events at a series of locations, and the subjects had to point to the location where a stimulus appeared two events ago. Thus, the *n*-back task resembles the delayed response task in that a series of items appear and the subject must distinguish the relevant from the irrelevant ones. The order of spatial stimuli determines the relevant location. Activation occurred in the caudal PF cortex (area 8) on the first task, in which order had no relevance, but no activation occurred in the mid-lateral PF cortex. However, on the *n*-back task, for which order is relevant, the activation also occurred in the mid-lateral PF cortex.

Gray et al. (2003) showed directly that the *n*-back task involves interference. They used a three-back task for faces and compared high-interference and low-interference conditions. The high-interference condition used the same set of faces for all stimulus presentations. The low-interference condition used novel faces either two or four trials back, as distractors. The subjects performed much more poorly when the distractor faces came from the same set as the target faces, as opposed to when the distractor faces were novel. In the same study, Gray et al. found more activation in the mid-lateral PF cortex, among other areas, in subjects who performed better on the high-interference condition.

Spacing trials

As in the imaging study of Gray et al. (2003), one can study interference by manipulating it directly. One can, for example, test monkeys on only one trial per day. Wilson et al. (1963) did that experiment and found that even without trial-to-trial interference, monkeys with large PF cortex lesions still performed at chance level on the delayed response task.

There are two possible explanations for this result. First, the monkeys may have failed to learn the rule that what they observed before the delay period determined what goal they should choose after the delay. Second, the lesions made by Wilson et al. included the ventral PF cortex and the orbital PF cortex. Subsequent experiments showed that

monkeys with combined lesions of the ventral and orbital PF cortex (Passingham 1971), or lesions of the orbital PF cortex alone (Meunier et al. 1997), had impairments on the delayed response task. If, as Chapter 4 discusses, the orbital PF cortex learns the associations between choices and outcomes, the loss of these associations could account for part of the impairment seen by Wilson et al. On this view, it could still be true that the mid-lateral PF cortex is needed to resolve interference from trial-to-trial, because the impairment that Wilson et al. reported could result from other factors. According to this account, the mid-lateral PF cortex is necessary for performing the delayed response task in the face of interference from previous trials. When there is no such interference, as in the experiment of Wilson et al., the orbital PF cortex is necessary for performing the task based on predicted outcomes.

Use of objects

Rather than simply reducing interference, one can also eliminate interference by using different items on each trial. Delayed response-like tasks can involve only a limited number of locations, but similar tasks can use an infinite number of objects or pictures. Levy and Goldman-Rakic (1999) presented three novel objects on each trial, and gave the monkeys an opportunity to pick one object. A delay followed, and after the delay the monkeys had to pick one of the other objects.

Petrides (1995) called this the ‘self-ordered’ task because the monkey can choose the order in which to pick the objects. Because we know that it does not matter whether the subject orders the objects or the experimenter does, we prefer to call it the ordered object task. Levy and Goldman-Rakic taught this task to monkeys and then made lesions that either included the mid-lateral and postero-lateral PF cortex, together, or the dorsal convexity of the PF cortex. Monkeys in both groups performed the ordered object task normally.

Yet Petrides (1995) found that monkeys with lesions of the dorsal PF cortex showed severe impairments on the ordered object task (Figure 6.4). As in the experiment by Diamond and Goldman-Rakic (1989), this result cannot be explained in terms of perseveration, and for the same reason.

In a later study, Petrides (2000) showed that monkeys with lesions of the mid-lateral PF cortex (area 46) or the dorsal convexity (area 9) also showed impairments on this task when pictures served as the stimulus material. And with a larger set of objects, ranging from three to five, the monkeys showed a larger impairment.

The study of Levy and Goldman-Rakic differs from those by Petrides in a critical way. Petrides re-used the same items across trials, and so the monkey had to base its choice on which object or picture it had touched most recently. In this task, Petrides created a high degree of trial-to-trial interference. By contrast, Levy and Goldman-Rakic used novel objects, and so avoided interference effects. Thus the lesions caused impairments in high-interference conditions but not in low-interference conditions. These findings support two related ideas: trial-to-trial interference causes the deficit that follows a lesion of the mid-lateral PF cortex and this area mitigates the interference in normal monkeys.

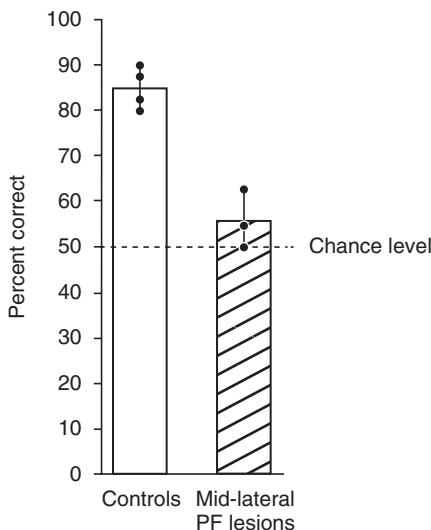


Fig. 6.4 Results from the ordered object task, also known as the self-ordered task. Percent correct for normal (control) monkeys (white bar) and lesioned monkeys (hatched bar). Filled circles indicate the performance of each subject, with a vertical line showing the range. Redrawn from Petrides M. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *Journal of Neuroscience* 15:359–75, © Society for Neuroscience, 1995, with permission.

Summary

In tasks involving objects, monkeys with lesions of the mid-lateral PF cortex perform normally when each trial uses different items; but when the experimenters use the same set of stimuli from trial-to-trial, lesioned monkeys perform near chance level. In the delayed response and delayed alternation tasks, of course, experimenters use the same set of places from trial-to-trial—and lesioned monkeys also perform near chance level. Thus a failure to resolve trial-to-trial interference could account for the impairment on the delayed response and delayed alternation tasks.

The results do not distinguish, however, among three possible explanations for the susceptibility to interference:

1. The monkeys might make errors in judging the temporal order of events.
2. They might not know the rules that guide task performance.
3. They might not compensate for interference by prospectively encoding the goal.

We discuss each of these possibilities, in turn, in the next three sections.

Temporal order

The first explanation suggests that monkeys with mid-lateral PF lesions have impairments in distinguishing which of the two stimulus events, such as a left cue versus a right

cue, occurred more recently. As a series of trial unfolds, they occur in a temporal order, and only one is the most recent. One can test the first explanation by requiring monkeys to choose between two items on the basis of the order in which occurred. The use of different items on every trial eliminates interference effects.

Petrides (1991) did this experiment, requiring the monkeys to choose the object that appeared earlier rather than later. He presented four objects in a given order and later presented two of the objects simultaneously as a choice. He used novel objects on each trial. The lesioned monkeys could choose correctly between the first item in the sequence versus any alternative or between the last item versus any alternative. But these choices tell us nothing because choosing the first stimulus always leads to reward, as does avoiding the last stimulus in the series.

In the key test, the monkeys had to choose between items that occurred in the middle of the series. In a four-item series, the second and third items occupy this middle ground. Petrides found that lesions of the dorsal part of the mid-lateral PF cortex (area 46) caused an impairment in distinguishing the items based on order, especially for the second and third items (Figure 6.5). He obtained similar results for a five-item series.

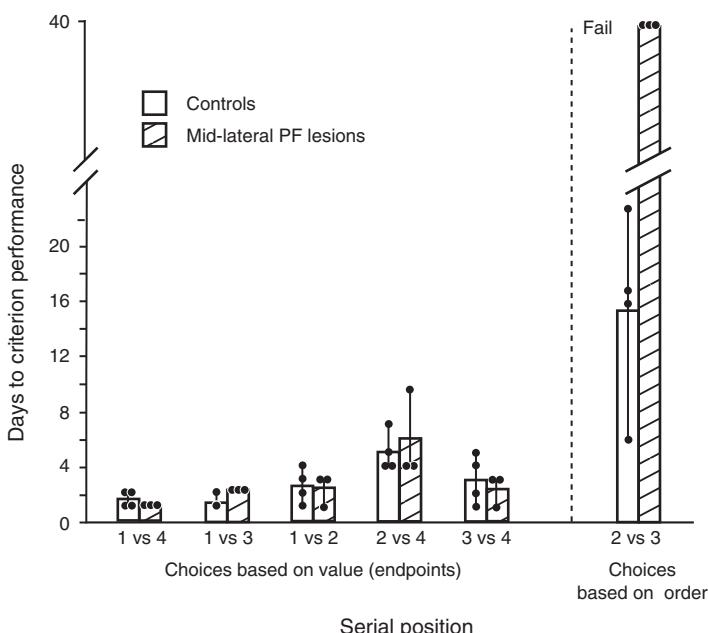


Fig. 6.5 Results from the serial order task. In the format of Figure 6.4, except that the ordinate plots the number of days to master the problem. Each pair of bars compares normal (control) monkeys (white bars) and lesioned monkeys (hatched bars) for choices between two items, based on their rank within a series of items [1 . . . 4]. The dashed vertical line separates choices involving endpoint items (items 1 or 4) from the choice that includes neither endpoint. For the latter, monkeys with lesions of the mid-lateral PF cortex did not master the problem within the limit of testing days (fail). Redrawn from Petrides M. Functional specialization within the dorsolateral frontal cortex for serial order memory. *Proceedings of the Royal Society – Biological Sciences* 246:299–306, © The Royal Society, 1991, with permission.

Monkeys can learn this task, but only with difficulty. Human subjects find it easy to learn tasks with long series of novel pictures. Milner et al. (1985) reported that patients with frontal lobectomies did poorly at choosing the picture that occurred more recently. It is unlikely that they failed because they did not know the rule, because on each trial the experimenters asked them to choose the more recent picture.

Of course, this impairment could result from any part of these large lesions. So Amiez and Petrides (2007) conducted an imaging experiment on people as they judged which of two stimuli had appeared earlier in a sequence. The activation occurred in the mid-lateral PF cortex.

The finding that single cells in the mid-lateral PF cortex encode order supports the lesion and activation studies. Ninokura et al. (2003) presented three coloured patterns in sequence, and the monkeys learned to touch them in that order. In the mid-lateral PF cortex, 43% of the cells with delay-period activity encoded the sequence in which the pictures had appeared. Funahashi et al. (1997) found similar results for spatial stimuli. Their monkeys had to choose two targets in the order they had appeared, and of the mid-lateral PF cortex cells that exhibited delay-period activity, 62% encoded stimulus order.

A possible mechanism for the encoding of order was suggested by a study by Warden and Miller (2007). They recorded in the mid-lateral PF cortex while monkeys performed a task in which they had to judge which of two pictures occurred most recently. The activity for the second picture exceeded that for the first picture, a property that may provide a mechanism for a judgement about order.

Summary

Impairments on the delayed response task could result from an inability to judge the order of events. Over a series of trials, visual events guide the choice of every possible goal, and only the last one is relevant to the current trial. This section reviews evidence that monkeys with mid-lateral PF lesions have an impairment in distinguishing the order of events. Likewise, cells in the mid-lateral PF cortex encode event order. Recall that Tsujimoto and Postle (2012) showed that when monkeys made frank errors in an oculomotor version of the delayed response task, they usually chose the goal that had been appropriate on the previous trial (Chapter 5).

Rules

Our second explanation for the impairment suggested that the lesioned monkeys could not learn or apply the task rule. To perform the delayed response task, monkeys must apply the following rule in some form: the location of the most recent visual event determines the current goal.

Monkeys can learn many rules of this kind, and we know that when monkeys learn a rule, cells in the mid-lateral PF cortex encode these rules, as they do in other parts of the PF cortex. Chapter 7 takes this issue up in some detail for the ventral PF cortex. For example, cells in the PF cortex have differential activity for conditional visuomotor rules and spatial rules (White & Wise 1999). Cells also encode the matching or nonmatching rule

(Wallis et al. 2001) and whether the matching rule involves colour or shape (Mansouri et al. 2006). Furthermore, PF neurons encode these rules prospectively, that is, in advance of their implementation (Wallis et al. 2001).

A study by Buckley et al. (2009) supports a role for mid-lateral PF cortex in the implementation of task rules. They tested monkeys that had learned two versions of the matching-to-sample task. In one version, monkeys matched according to shape; in the other, they matched according to colour. On each trial, they chose among three stimuli: one matched the sample by colour, another matched by shape, and one matched by neither feature. Once the animal reached criterion on one rule, the experimenters cued a switch to the other rule with feedback consisting only of reward or nonreward.

The monkeys learned these rules before surgery, and monkeys with lesions of the mid-lateral plus postero-lateral PF cortex could relearn and switch between them. However, if after they had relearned one of the rules, they encountered a longer-than-usual intertrial interval, their performance fell to 50% correct (Buckley et al. 2009) (Figure 6.6). This level of performance corresponds to the chance level, provided that one ignores the choice that followed neither rule. This finding suggested to Buckley et al. that the mid-lateral PF cortex functions in the maintenance of the current task rule in memory.

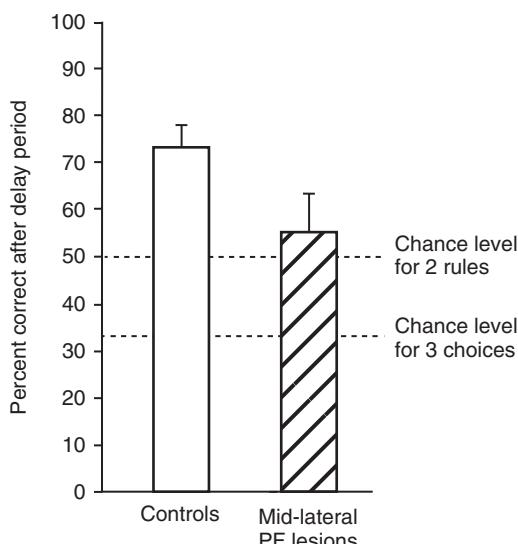


Fig. 6.6 Performance of monkeys on a rule task similar to the Wisconsin card sorting task. Monkeys performed the matching-to-sample task, matching either by colour or shape, alternating in blocks of trials. Percent correct performance for normal (control) monkeys (white bar) and monkeys with lesions of the mid-lateral PF cortex (hatched bar) after the delay period increased from 6 s to 11 s. Dashed lines show chance levels of performance for the task as a whole (33% correct) and for the choices that followed one of the two rules (50% correct). Error bars: SEM. Modified from Buckley MJ, Mansouri FA, Hoda H, Mahboubi M, Browning PGF, Kwok SC, Phillips A, Tanaka K. Dissociable components of rule-guided behavior depend on distinct medial and prefrontal regions. *Science* 325:52–8, © 2009 AAAS, reprinted with permission.

Additional evidence indicates that the dorsal PF cortex, including lateral area 9, mid-lateral, and postero-lateral PF, plays a role in learning rules. One of the rules on the delayed alternation task is that, if the monkey makes an error, the reward will be on the same side on the next trial. This rule applies because the standard delayed alternation task uses a correction procedure, which helps the animal master the task. This means that the monkeys can adopt a strategy called ‘lose-shift’ in order to help them in solving the problem. According to this rule, when the choice of one goal fails to pay off, that goal should be rejected on the next trial.

Passingham (1975) analysed the errors made on the delayed alternation task by monkeys with dorsal PF cortex lesions. Of the three animals tested, one took 420 trials to learn the ‘lose-shift’ strategy, one took 900 trials, and one failed to learn it in 1000 trials. By comparison, two normal monkeys took 240 and 60 to learn the same strategy, and one monkey needed no training to apply the rule. So the monkeys with dorsal PF lesions have a severe impairment in acquiring the ‘lose-shift’ strategy.

Once the monkeys had learned the ‘lose-shift strategy’ for correction trials, they need to learn the rule for the regular trials on the delayed alternation task. This rule defines the task: the goal on each trial should be the place that did not have the reward on the previous trial. In other words, they have to learn a ‘win-shift’ rule. Compared to rules such as ‘win-stay’ or ‘lose-shift’, the ‘win-shift’ rule has an arbitrary nature. Reinforcement makes it more likely that the animal will choose a rewarded goal, and the ‘win-stay’ rule supports this principle. Likewise in reverse for ‘lost-shift’. The ‘win-shift’ rule opposes the recent reinforcement history, however. In the study by Passingham (1975), monkeys with dorsal PF lesions failed to learn the ‘win-shift’ rule in 1000 trials.

Summary

Impairments on both the delayed response and delayed alternation tasks might reflect a failure to apply the appropriate task rule. The delayed response task uses the rule that the most recent visual event determines which goal the monkey should select: its choice should match the location of that event. The delayed alternation task uses the rule that that most recent goal choice should be rejected in favour of the alternative.

This possibility has an indirect relationship with the ideas about credit assignment that Chapter 4 discusses for choice–outcome associations. Monkeys with orbital PF lesions have impairments in learning choice–outcome associations on the basis of a single event. It might be that monkeys with lesions of the mid-lateral PF cortex have a related problem: perhaps they cannot implement a rule that uses a single event (the most recently cued location) to generate a current goal.

Prospective coding

Earlier we suggested a third explanation for lesion effects on the delayed response task. Perhaps monkeys with mid-lateral PF cortex lesions can learn the rule, but cannot compensate for interference in memory by prospectively coding the goal in memory. On this view, the short-term memory for the current goal wards off the effects of trial-to-trial interference.

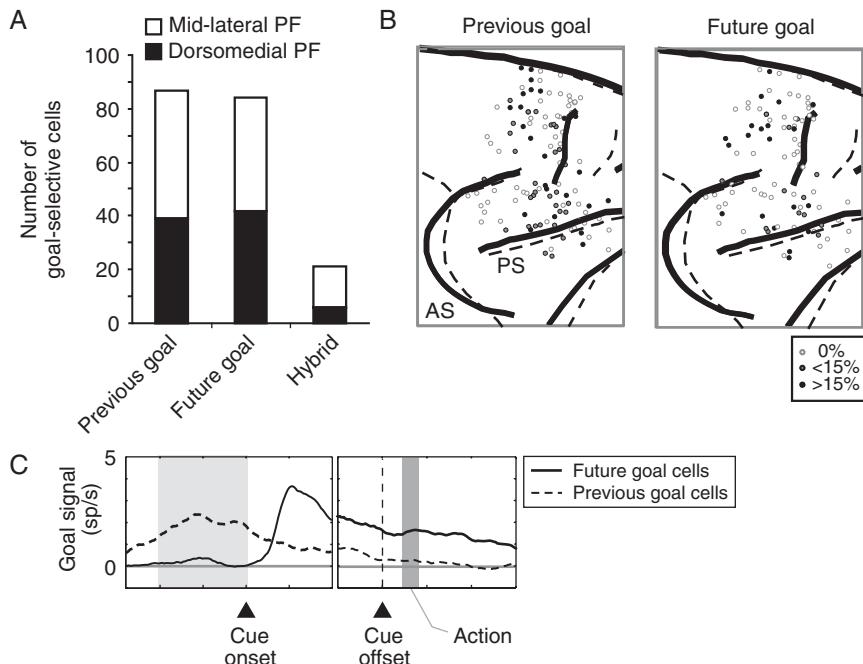


Fig. 6.7 Separate encoding of previous and current goals. (A) Most PF neurons encoded either the current goal or the previous one, with only a few encoding both (hybrid). These data show that PF cortex cells encode both retrospective and prospective memories. (B) Locations of cells encoding previous or current goals. Unfilled circles show sites without such coding; light and dark grey circles show sites with less than 15% or greater than 15% of the neurons showing these properties, respectively. The dashed lines show the sulci from a second monkey, superimposed on those from the first (solid sulcal lines). (C) Goal signals for previous and current goals at the population level. The dashed line shows the mean signal for retrospective coding; the black line shows the mean signal for prospective coding. Adapted from Genovesio A, Brasted PJ, Wise SP. Representation of future and previous spatial goals by separate neural populations in prefrontal cortex. *Journal of Neuroscience* 26:7305–16, © Society for Neuroscience, 2006, with permission.

In a study already mentioned, Genovesio (2006a) recorded neuronal activity in both parts of the dorsal PF cortex (area 46 and area 9) (Figure 6.7B). On every trial, the monkey had to choose among three spatial goals: up, left, and right from the fixation point. Also on every trial, the monkey had to use the retrospective memory of its most recent goal choice to make a choice of the current goal (prospective memory) (Figure 6.7C).

Genovesio et al. found two separate populations of cells in the dorsal PF cortex. One encoded the location of the goal on the previous trial and the other encoded the location of the goal on the current trial (Figure 6.7A). Only a few cells encoded locations more generally (hybrid cells). The effect of a lesion might therefore render animals unable to distinguish between past and current goals because of a failure in prospective coding. An inability to distinguish the locations of previous goals from the current one, alone, would account for the deficit on the delayed response task.

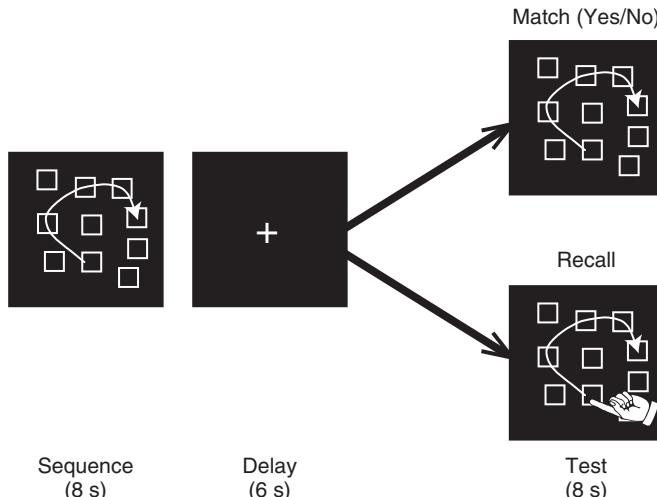


Fig. 6.8 Matching and recall tasks used in imaging experiments. After the presentation of a sequence of locations (left, curved arrow), and a delay period (middle), the subjects needed to perform one of two tasks (right). In the top fork, the subjects see a sequence of spatial cues and had to report whether it matched the one presented originally, called the matching condition. In the bottom fork, the subjects had to reproduce the sequence originally observed, called the recall condition. Only in the recall condition did subjects plan movements to a series of goals during the delay period. Reproduced from Pochon JP, Levy R, Poline JP, Crozier S, Lehéricy S, Pillon B, Deweer B, Le Bihan D, Dubois B. The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. *Cerebral Cortex* 11:260–6, © 2001; with permission from Oxford University Press.

Studies with human subjects also provide evidence for prospective coding in the mid-lateral PF cortex. Pochon et al. (2001) studied activations while subjects performed two tasks that tested memory for a sequence of spatial locations. Visual stimuli appeared in a sequence of up to five locations, and after a delay of 6 seconds the experimenters assessed memory in one of two ways (Figure 6.8). First, they presented another sequence after the delay, and the subjects had to press a button to report whether it matched the original sequence. Second, after the delay period the subjects had to point to each location in the order that they had appeared. They called the first condition *matching* and the second condition *recall*.

In the matching condition, the subjects could not know during the delay period whether they would press the button. This condition thus required that they remember the sensory cues (retrospective memory) but precluded the planning of future actions (prospective coding). By contrast, in the recall condition, the subjects could prepare their actions during the delay (prospective coding).

Pochon et al. found no significant delay-period activation in the mid-lateral PF cortex in the matching condition, despite the need for remembering a sequence of cued locations. In the recall condition, by contrast, they found highly significant delay-period activation in that area (Figure 6.9). Both the matching and recall conditions required

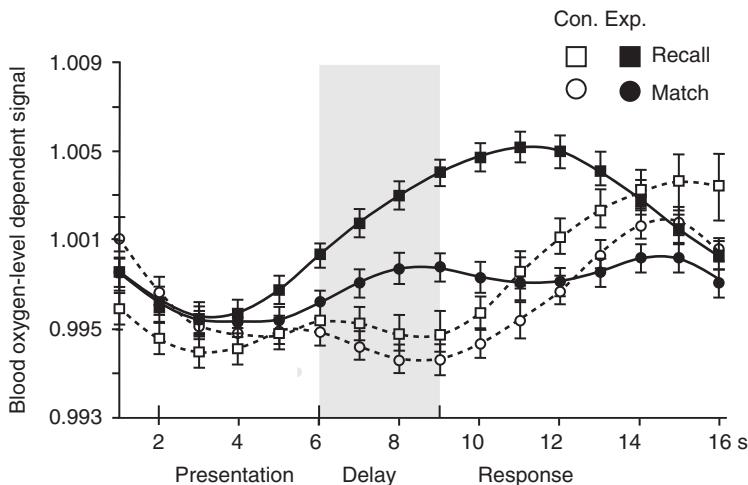


Fig. 6.9 Imaging activations during the tasks illustrated in Figure 6.8. Filled squares: recall condition; unfilled squares: control for recall condition; filled circles: matching condition, unfilled circles: control for matching condition. Error bars: S.E.M. The greatest delay-period activation, which peaked afterwards at 11 s, occurred when subjects planned movements to a sequence of spatial goals with hand movements (recall task). Reproduced from Pochon JP, Levy R, Poline JP, Crozier S, Lehéricy S, Pillon B, Deweer B, Le Bihan D, Dubois B. The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. *Cerebral Cortex* 2001; 11:260–6 with permission from Oxford University Press.

retrospective spatial memory. The conditions differed in that the recall condition required the planning of a future sequence of goals or actions: prospective coding.

Pochon et al. also found delay-period activation in the caudal PF cortex and in the posterior parietal cortex. However, in these areas activation occurred on both the matching and recall tasks, with no difference between the tasks. Thus the mid-lateral PF cortex differs from both caudal PF and posterior parietal cortex in lacking significant activation for retrospective coding (during matching), indicating that what is special about PF activation involves prospective coding.

The same researchers followed-up their experiment by devising a task with two delay periods (Volle et al. 2005). The subjects again saw a series of locations that they had to remember. Only the second delay period permitted the prospective coding of future goals. Significant delay-period activation occurred in the mid-lateral PF cortex during the second delay period but not the first. In a control task, a new sequence continuously appeared on the screen during the second delay-period, and the subjects had to prepare to execute that sequence instead of the original one. If the delay-period activation reflected the plan for a future sequence of goals, rather than the memory of a previous sequence of cues, then one should see the same activation on this control task as on the main task, and this is just what Volle et al. found.

One could object that the apparent lack of delay-period activation during the first delay period is due to the insensitivity of the BOLD signal. And indeed Goldman-Rakic and

Leung (2002) raised this objection when Rowe et al. (2000) reported the absence of delay-period activation on a spatial memory task. In the task used by Rowe et al. the subjects could remember stimuli during the delay period, but they could not prospectively encode their goal.

It is possible to test whether the lack of delay-period activation results from insensitivity of the methods. Simal and Curtis (2008) used specialized coils to improve the sensitivity, and they could detect delay-period activation rostrally in the dorsal PF cortex (the superior frontal sulcus) on a spatial matching task. This finding agrees with the results of cell recording in monkeys. As mentioned earlier, Genovesio et al. (2006a) found a sub-population of cells in this area that encodes retrospective memories. So the imaging results cannot be taken to demonstrate the absence of such activity. Instead, they suggest a predominance of prospective over retrospective activation in the mid-lateral PF cortex (area 46), probably based on a greater degree of synaptic activity (Chapter 1).

In view of the cells that retrospectively code locations in the mid-lateral PF cortex, a critic of our view could still claim that this activity supports retrospective working memory. Lesion results can test this claim. Ferreira et al. (1998) tested patients with dorsal frontal cortex lesions on the tasks later used by Pochon et al. They found that the patients had no impairments in the matching condition, the condition that did not involve the prospective coding of goals. The reason is, presumably, that cells in the posterior parietal cortex can support the memory of locations. However, as expected from the imaging results, the same patients had impairments in the recall condition, the condition that involved the prospective coding of goals (Ferreira et al. 1998). Bor et al. (2006) also report that patients with dorsal frontal lesions have impairments in recalling sequences from an array of locations. Thus all of the studies in this section point to the importance of prospective coding in the function of the mid-lateral PF cortex.

Prospective coding and interference

We have suggested that prospective coding compensates for interference in memory. The concept of accumulator networks, as introduced in Chapter 3, explains how this could work. Chapter 5 uses this concept to explain top-down attention in terms of a bias among competing representations. On this view, the influence of the PF cortex acts something like a ‘thumb on the scale’ to provide an advantage for one kind of sensory representation versus another as they integrate ‘evidence’ toward a threshold. In the delayed response task, the most recent relevant visual event serves as the crucial ‘evidence’ for an accumulator network representing the goal appropriate for that event. If the most recent cue or food appears to the right, for example, this event provides sufficient ‘evidence’ for the generation of a goal to the right. The difference between the top-down attention of Chapter 5 and the top-down attention of the delayed response task is that the former involves sensory processing and the latter involves goal generation. For successful performance, the memory of the most recent event, the cue to the right in this example, must prevail in the competition with the memory of less recent events, such as earlier cues to the left.

In a study with human subjects, Sakai et al. (2002a) tested this proposal by deliberately introducing distractors into the task. The subjects saw a sequence of five spatial locations,

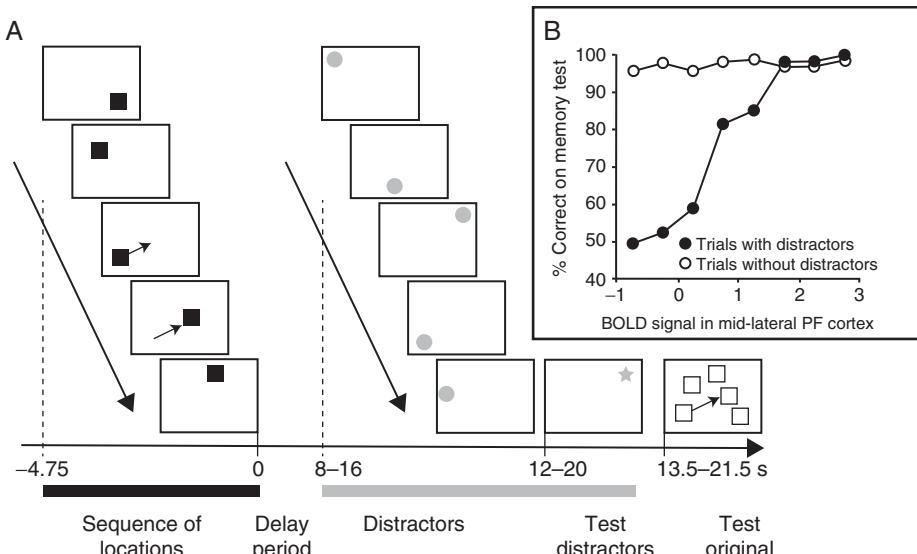


Fig. 6.10 (A) Spatial memory task used in an imaging experiment. The filled black squares indicate an original sequence of spatial cues; the filled grey circles represent a sequence of distractors. Some trials lacked distractors. The grey star represents a probe for the distractor items. The subjects had to say whether this location was one of those in the distractor series. In this example, it was (the third from the top). The arrow in the bottom right panel shows a possible transition from one location to another. The subjects had to say whether this transition occurred in the original sequences. In the example illustrated, it did, as noted by the arrows in the third and fourth panels in the left column (not seen by subjects). (B) Performance accuracy as a function of mid-lateral PF cortex activation (BOLD signal) during the delay period. Filled circles: trials with distractors; unfilled circles: trials without distractors. The subjects did not know in advance whether distractors would appear. Modified from Sakai K, Rowe JB, Passingham RE. Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nature Neuroscience* 5:479–84, © 2002, Nature Publishing Group.

and on half the trials five more distractor locations appeared after a variable delay period (Figure 6.10A). After presentation of the distractor items, the experimenters tested the subjects' memory: first for the order of the distractor items and then for the order of the original items.

Although the matching procedure tests memory, the use of long delays forced subjects to rehearse the items. Tremblay et al. (2006) showed that, when allowed to do so, subjects often do this by moving their eyes from one location to another. People can, of course, remember locations without employing this strategy, but rehearsing the locations in this way helps them retain the information, as shown by the fact that if subjects move their eyes to irrelevant locations during the delay, they do not recall the items as well (Guerard et al. 2009).

Sakai et al. (2002a) used long delays and found significant delay-period activation in the mid-lateral PF cortex, even though a matching procedure was used. This supports the idea that their subjects rehearsed the sequence. Leung et al. (2002) also used a matching procedure with long delays (18 or 24 seconds), and they too found delay-period

activation in this area. The longer the delay, the greater the likelihood of being distracted, and so the greater the incentive to rehearse.

In the study by Sakai et al. (2002a), the delay varied between 8–16 seconds, and memory for the locations was not tested until 5 seconds later. Furthermore, the subject did not know whether distractor items would be presented on any given trial. Figure 6.10 shows that on trials with distractors, the degree of delay-period activation correlated closely with the accuracy of the subjects' responses (Figure 6.10B). These results suggest that delay-period activation serves to protect memories from distraction.

The study just described used locations as stimuli. Sakai and Passingham (2004) subsequently used letters as stimuli in order to manipulate the degree of interference. They did so by using distractor items that were either the same as the memory items or different. Like the earlier study, the experimenters presented sequences of five letters to be remembered, followed by a delay. They then presented as distractor items either five more letters or five numbers and later tested for the original letters. Obviously, the distractor letters produced more interference than the numbers.

As in the earlier study, Sakai et al. (2002b) found delay-period activation in the mid-lateral PF cortex. Activation also occurred during the retrieval of the original letter sequence during the memory test. Importantly, the high-interference condition (letter distractors) produced significantly greater activation than did the low-interference condition (number distractors). This finding supports the idea that that prospective activation in the mid-lateral PF cortex can help to protect memories from interference.

Summary

Our third possible explanation for susceptibility to interference invoked the concept of prospection. This section presents evidence that prospective coding, in the form of both cell activity and regional activation, occurs in the mid-lateral PF cortex. We do not deny that a proportion of cells in this area reflect retrospective coding during delay periods, but at least in the imaging data prospective coding seems to predominate.

We propose that prospective coding in the mid-lateral PF cortex compensates for interference in memory. With greater delay-period activation, memory in the face of interference becomes more accurate. And with more interference, activation increases in the mid-lateral PF cortex at the time of recall. These findings support the idea that monkeys with lesions of the mid-lateral PF cortex succumb to interference because they cannot prospectively encode the current goal.

Taking the last three main sections, together, we conclude that lesions of the mid-lateral PF cortex cause impairments on the delayed response and delayed alternation tasks for one or more of three related reasons. First, they might have lost the ability to distinguish the most recent relevant event from earlier ones. Second, they might be unable to learn or implement the task rules, which call for using the most recent event to choose the current goal. And third, they might be unable to compensate for interference from less recent trials by prospectively encoding the current goal. We call these three possibilities the order-coding, rule-coding, and prospective-coding accounts, respectively.

Generation of goals

We do not know which of the three possibilities—order-, rule-, or prospective-coding—accounts for the delayed response impairment after mid-lateral PF cortex (area 46) lesions, and perhaps they all contribute to it. Regardless, a key factor is the requirement on all of these tasks is that monkeys must vary their choice of goal from trial to trial. Experiments in human subjects can have the same requirement.

We have long known that if subjects generate a series of actions, varying them as randomly as they can, the mid-lateral PF cortex becomes activated. In a study by Deiber et al. (1991) the subjects moved a joystick in one of four directions, and in a study by Frith et al. (1991) they moved one of two fingers. In both studies the subjects decided which movement to make on each occasion. This led to the suggestion that these tasks involve ‘free selection’ (Playford et al. 1992) or ‘willed action’ (Frith et al. 1991).

Since these studies, many more have appeared, and all have found the same result (Spence & Frith 1999; Frith 2000). Furthermore, as Rowe et al. (2005) have shown, not only does the mid-lateral PF cortex become activated when subjects generate finger movements, but such activation does not occur when the direction of an arrow instructs the movement.

Given that subjects vary their movements across trials, they need to pay attention to their last few movements. Thus, as on the delayed response and delayed alternation tasks, the choice on each trial depends on previous choices.

A neurophysiological study by Barraclough et al. (2004) likewise required monkeys to generate a series of choices between a left and a right target. A computer program determined whether a choice would be rewarded, and it changed over time to encourage the monkey to switch targets, much like the object reversal tasks that Chapter 4 reviews. The authors recorded in the mid-lateral PF cortex and found a significant proportion of cells that encoded the choice on the previous trial, along with other information. For example, a cell might encode a goal to the right only when the previous goal was to the left. Many cells also encoded whether the previous choice had produced a reward. These cells integrate information about the previous choice and its outcome. Barraclough et al. concluded that they update a value function that determines the current choice, much like the cells in the orbital PF cortex that Chapter 4 discusses.

Tsujimoto and Sawaguchi (2004a, 2005) found evidence that cells in the mid-lateral PF encode combinations of goals and outcomes, and Tsujimoto et al. (2011a) obtained similar results. The task in the latter study involved a visual cue that provided an instruction to shift from or stay with the previous spatial goal. As illustrated in Figure 6.11, the cell at the top encoded the previous goal, the next one down encoded the future goal, the next one encoded the conjunction of the strategy and the goal, and the bottom one encoded the strategy immediately after the cue and then later changed to encode the current goal.

Thus the cell-recording results, like the imaging results, support the proposal that the mid-lateral PF cortex plays a role in generating goals. These results also point to the

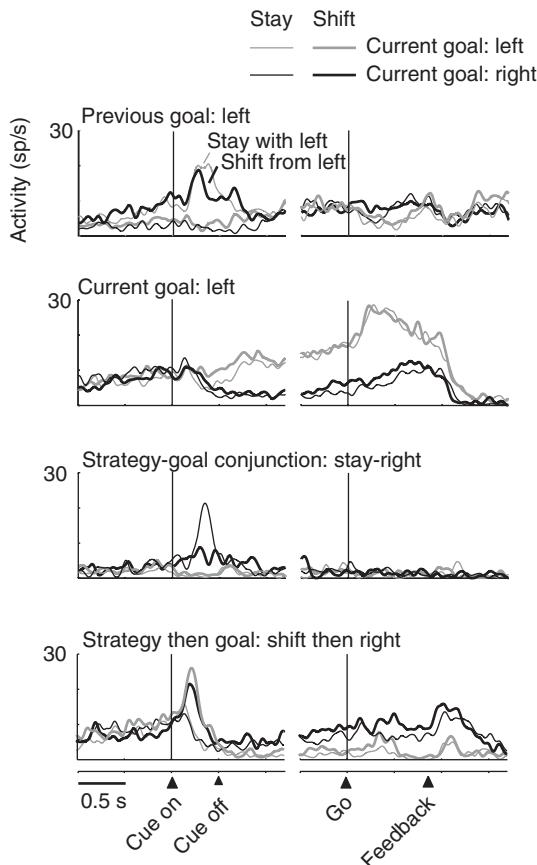


Fig. 6.11 Patterns of mid-lateral PF cortex activity in a cued-strategy task. Each of the four cells shows different encoding properties. Thin lines show average cell activity on trials with stay cues; thick lines show activity for shift cues. Grey lines show activity on trials that lead to choosing a current goal to the left; black lines show activity for current goals to the right. The combination of cue type and previous goal determines the current goal on each trial. For example, for the cell at the top, the thin grey line shows activity for trials with stay cues, a previous goal to the left, and therefore a current goal to the left. The top cell also prefers trials with shift cues, a previous goal to the left, and therefore a current goal to the right (a shift). The common feature of cell activity is that it encodes a previous goal to the left. The next cell down prefers a current goal to the left (grey lines); the next one prefers the conjunction of the stay strategy and a current goal to the right (thin black line); the bottom cell encodes the shift strategy during the cue period (thick lines), but later in the trial encodes the choice of the rightward current goal (black lines). Data from Tsujimoto S, Genovesio A, Wise SP. Comparison of strategy signals in the dorsolateral and orbital prefrontal cortex. *Journal of Neuroscience* 31:4583–92, © 2011, Society for Neuroscience.

importance of a series of events, including the goals and cues that occur on successive trials. Often, the goal on one trial depends on what happened on previous trials.

If it is critical that the order be varied from trial-to-trial, a simple prediction emerges: activity and activation should be absent on the first trial of such tasks. First, nothing on the first trial varies from a previous trial. Second, the choice on the first trial does not depend on any events from a previous trial. On the first trial, no recent events provide a context for making a choice.

Accordingly, Rowe et al. (2010) examined activation on the first trial of a series of finger movements. As expected, activation occurred in the mid-lateral PF cortex in this task, as averaged over many trials. But, crucially, no significant activation occurred in this area on the first trial. And this result did not reflect a lack of statistical power or the sensitivity of the method; when the authors selected a single trial in the middle of the series, they could detect significant activation in mid-lateral PF cortex.

If this activation plays a critical role in the generation of a varying series, patients with large lesions of the PF cortex should be impaired on ‘free selection’ tasks. Johns (1996) collected a group of 20 such patients and asked them to generate a series of movements, using a joystick that could be moved in four directions. Compared with control subjects, the patients produced a more stereotyped and less random sequence of movements.

The study of Johns et al. involved large lesions, but imaging and repetitive transcranial magnetic stimulation (rTMS) can locate the critical area more accurately. Jahanshahi et al. (2000) observed activation in the mid-lateral PF cortex when subjects generated a random series of numbers, with greater activation for more random series. In a subsequent study (Jahanshahi & Dirnberger 1999), the same investigators applied rTMS to this area to disrupt its activity, and this kind of lesion caused the series to become more stereotyped. Thus the mid-lateral PF cortex seems to play a necessary role in making choices that vary from trial to trial.

Summary

This section, like the previous three, reviews evidence that the mid-lateral PF cortex generates goals based on event order and prospectively encodes goals. First, activation occurs in the mid-lateral PF cortex when people generate a series of goals. Second, the activation reflects the need to produce a varying series of goals. And third, it seems to be absent on the first trial of a series.

Planning a sequence

In the tasks described in the previous section, the subjects generate a series of goals across trials. However, we do not always know whether they simply generate the next goal on each trial or whether they plan a series of goals beforehand.

To find out, Averbeck et al. (2006) taught monkeys sequences of three eye movements, which they learned by trial and error. Monkeys can learn such a short sequence within just a few trials. The authors recorded in the postero-lateral PF cortex, rostral to the frontal eye field (FEF), and found neurons that encoded the specific sequence that the

monkey planned just before it made the movements. Using a simple decoding algorithm, they could predict when the monkey would make errors and what that error would be. These results imply that the monkeys planned a sequence of movements in advance.

In a related study, Shima et al. (2007) taught monkeys sequences of movements. In their experiment, the monkeys made reaching movements rather than eye movements, and they manipulated a handle which they could turn, push, or pull. Four movements composed each sequence. On each day, the monkey learned a sequence by following visual cues, and then repeated it from memory. Shima et al. recorded from the postero-lateral PF cortex as the monkeys prepared to produce various sequences. As usual, a delay period intervened prior to the execution of the sequence.

Of the task-related cells, over 40% showed delay-period activity. Shima et al. (2007) trained the monkeys on eleven sequences in all, and they could compare sequences with similar patterns. A pattern, in this sense, refers to the transitions in a sequence. For example, one pattern consisted of a double repeat, AABB, where A and B represent different elements in the sequence. Another pattern consisted of alternation: ABAB. Both sequences consisted of the same elements in the same proportions, but they differed in the number of transitions. And, of course, A and B differed from sequence to sequence and there was a third stimulus besides.

Of the cells that showed differential activity from sequence to sequence, and did so during the delay period, over half had similar activity for sequences with similar patterns. So, for example, the authors illustrate a neuron that encoded the double-repeat sequences ‘turn, turn, push, push’ and ‘pull, pull, turn, turn’ but did not encode the repeating sequence: ‘turn, turn, turn, turn’ or ‘pull, pull, pull, pull’. This cell had a preference for the pattern AABB over AAAA. Shima et al. interpreted this result as the encoding of sequences categories, such as double repeats (AABB), alternation (ABAB), or repetition (AAAA). Of the cells with delay-period activity, roughly half showed category-specific activity (Figure 6.12). Shima et al. found more of these cells dorsal to the principal sulcus than ventral to it.

In the sequences considered so far, the experimenter specified the order of elements in a sequence. But one can modify the task so that the monkey starts with a goal, and must work out a sequence of elements needed to achieve it. So, for example, Mushiake et al. (2001) presented monkeys with a visual maze (Figure 6.13), and the task required them to use a handle to move a cursor through the maze to a final goal.

Once the monkey learned a successful sequence of movements, the experimenters introduced a new visual obstacle so that the monkey had to plan a new route. Mushiake et al. recorded activity from mid-lateral PF cortex, both dorsal and ventral to the principal sulcus, and they focused their analysis on a delay period prior to movement. During the delay period, cells encode current goals. If achieving the final goal requires a sequence of three subordinate goals, different subpopulations of cells code for each of them (Mushiake et al. 2006). By manipulating the spatial transform between handle and cursor movements, Mushiake et al. could test whether a particular cell encodes a subordinate goal or a particular limb movement. For example, a handle movement to the left could

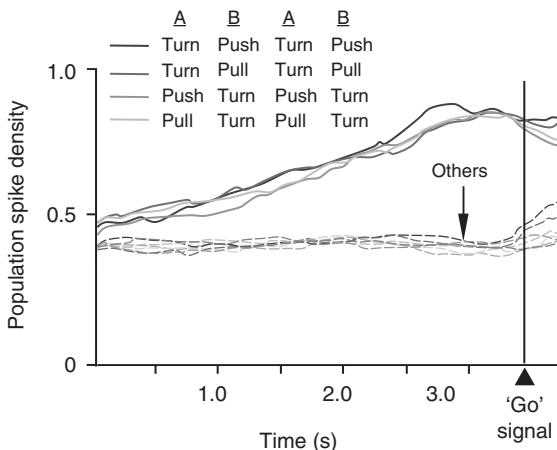


Fig. 6.12 Abstract sequence coding in a dorsal PF cortex cell. Solid lines show the preferred sequences for this neuron, all of which follow an alternating pattern: ABAB, with different movements composing the sequence. Dashed lines show sequences that do not follow this alternating pattern. Modified by permission from Macmillan Publishers Ltd. Shima K, Isoda M, Mushiake H, Tanji J. Categorization of behavioural sequences in the prefrontal cortex. *Nature* 445:315–18, © 2006, Nature Publishing Group.

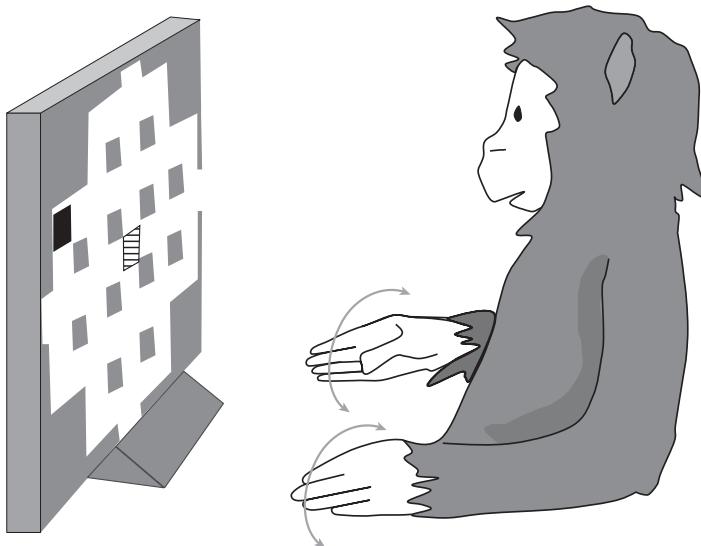


Fig. 6.13 Visual maze task. The monkey needed to make hand movements that drove a cursor from its current position on a trial (grey square) to a final goal (black square). The experimenters could change to hand movement that produced a given cursor movement. Redrawn from Mushiake H, Saito N, Sakamoto K, Sato Y, and Tanji J. *Cognitive Brain Research* 11:165–9, © 2001, with permission from Elsevier.

cause the cursor to move either to the left or to the right, depending on the spatial transform in force at the moment. And, as expected, most of the cells code for the goal rather than the movement.

To solve the problem posed by the maze task, the monkey had to calculate both subordinate and final goals. Cells in the mid-lateral PF cortex code for one, the other, or both (Saito et al. 2005). This made it possible for Sakamoto et al. (2008) to isolate pairs of cells, one coding for the subordinate goal and the other for the final goal. The synchrony in discharge peaked when a transition occurred between a neuron encoding a subordinate goal and another encoding the final goal. Likewise, in a task that required the use of previous goals to choose current ones, Tsujimoto et al. (2008) found activity correlations between cells encoding current goals and those encoding previous ones. These correlations strengthened when monkeys shifted from a previous goal compared to when they stayed with that goal.

If the mid-lateral PF cortex plays a necessary role in planning a series of goals, monkeys with lesions in this area should show impairments on such tasks. Passingham (1985a) tested monkeys on a spatial search task that had been devised by Collin et al. (1982). The monkey sits in front of 25 doors, and a peanut lies behind each door. The monkey simply has to reach for and open the doors, one-by-one, and retrieve the peanuts. We call this the 25-door search task.

Because the doors are opaque, the task requires the monkey to reach for targets that it cannot see. It pays the animal to open each door once and only once because the experimenters replace the peanuts only after a long sequence of reaches. Normal monkeys quickly learned the task. Monkeys with lesions of the mid-lateral and postero-lateral PF cortex, by contrast, more often returned to doors that they had already opened. Their search patterns showed severe disorganization.

But this disorganization does not necessarily reflect an impairment in planning. It could result from a failure to remember which doors they had already opened. Owen et al. (1990, 1996b) ruled out this explanation in two studies of lesion effects. They tested patients on a computerized version of the spatial search task. Patients with frontal lobectomies were impaired; like the monkeys, they tended to return to boxes that they had already tried. But Owen et al. also measured the consistency of their search pattern. They reasoned that touching the boxes in a regular, well-organized sequence reduces the load on memory. The patients with frontal lesions showed less regularity in which box they chose to start their search. Since this was the first choice, the irregularity cannot be attributed to forgetting previous choice in a series, and so a memory account of their results can be ruled out.

One advantage of searching in a regular way is that it decreases the need for working memory. Taffe and Taffe (2011) developed a ‘strategy score’ for macaque monkeys performing the spatial search task. The monkeys acquired the strategy of minimizing the distance between movements, and they made errors when they failed to use this strategy. The experiment has yet to be done, but based on the results from the 25-door search task we expect that monkeys with lesions of the mid-lateral PF cortex would have a very poor strategy score.

We touched on a key feature of such reaching movements in Chapters 2 and 5. There we explained that after the evolution of the fovea, primates developed a new way of reaching, one that computed both current reach targets and the current position of the hand in a fixation-centred coordinate frame (see Figure 5.3). We propose that after anthropoids evolved a mechanism for reaching in fixation-centred coordinates, this system became necessary for reaching to targets in an orderly sequence, especially for invisible targets. For reaching to visible targets, premotor and parietal mechanisms suffice and so lesions of the PF cortex do not affect this behaviour. These ideas become important when we later consider why the mid-lateral PF cortex plays a necessary role in the delayed response task in anthropoids but not in other mammals (Chapter 10).

Summary

Previous sections suggest: (1) that the mid-lateral PF cortex generates goals based on a context provided by the order, timing, and location of events, and (2) that it could do so through order-coding, rule-coding, or prospective-coding. This section extends this idea to a series of goals. In addition to concrete goals, such as places, activity in the mid-lateral PF cortex reflects the abstract structure of a sequence. Thus the mid-lateral PF cortex represents both concrete and abstract goals, and it does so both for single goals, as they vary from trial to trial, and for sets of goals, as they develop in structured sequences. Humans and monkeys with damage to the mid-lateral PF cortex show inefficiencies in organizing sequences that cannot be attributed to impairments in memory.

Later, in Chapter 8, we suggest that the PF cortex can encode abstract representations because it lies at the apex of a goal hierarchy. At successive stages in that hierarchy, higher-order cells can put together information from lower-order ones. In this way, the PF cortex can encode abstract representations of goals. The next section argues that the PF cortex also encodes representations of the current context.

Conjunctions and the current context

In previous sections, we have argued that the current context can be specified by the order of events in a series and by their spatial location. But other information contributes to current context, and the dorsal PF cortex encodes these aspects of visual events, as well.

Time intervals

The duration of time intervals, like the order of events in time, plays a major role in establishing a behavioural context. Cells in the posterior parietal area LIP encode the length of a temporal interval (Leon & Shadlen 2003), and this area projects to the dorsal PF cortex.

One would therefore expect to find activity in the PF cortex that reflects time intervals. In a recent study, Yumoto et al. (2011) recorded from the cortex of lateral area 9. A light appeared for a specified duration, and the monkeys were trained to report that time interval later by pressing a button when the same interval had elapsed. They found two populations of neurons. One population of cells became active after the specified time had elapsed. Genovesio et al. (2006b) found a similar result when the monkeys did not have

to report the time interval. Yumoto et al. also found cells that became active when the monkeys reproduced the time interval in the absence of external cues.

One would therefore expect monkeys with lesions of lateral area 9 to be impaired at reproducing time intervals. Passingham (1978) trained monkeys to report whether they had pressed a key one or five times, and Manning (1978) trained monkeys to report whether they had pressed a lever 32 or 64 times. Lesions of the dorsal PF cortex caused impairments in both tasks. These impairments might reflect difficulties in counting, but an impairment in timing seems more likely.

In the study by Passingham (1978), monkeys with lesions in the mid-lateral and postero-lateral PF cortex alone performed normally. This finding suggests that removal of the dorsal convexity cortex (lateral area 9) caused the impairment. And, in agreement with this suggestion, Yumoto et al. (2011) found that inactivation of the lateral area 9 caused monkeys to make errors in reporting time intervals.

The cell activity reported in the study by Yumoto et al. reflected the time interval alone. But one can also find activity that reflects the conjunction between the identity of objects and the duration for which they are presented. Genovesio et al. (2009) trained monkeys to discriminate relative durations and recorded from cells in the mid-lateral PF cortex. A blue circle and a red square appeared at the monkey's fixation point, and they lasted for differing durations. After a delay period, the two stimuli reappeared simultaneously, one to the left and one to the right. In order to receive a reward, the monkey needed to choose the one that had lasted longer. Genovesio et al. found cells in the dorsal PF cortex that encoded conjunctions between stimulus features and relative duration. For example, many cells encoded that the blue stimulus had lasted longer.

Distance

We mentioned cells in the posterior parietal cortex encode time intervals (Leon & Shadlen 2003). And some cells there encode the length of bars (Tudusciuc & Nieder 2007). So Genovesio et al. (2011) recorded activity in the mid-lateral PF cortex while monkeys performed a distance discrimination task. They used the same stimuli as in the duration discrimination task just mentioned: a blue circle and a red square. One stimulus appeared at some distance above a reference point, and the other stimulus appeared at a different distance below it. The monkey needed to report which stimulus had appeared farther from the reference. Some cells coded absolute distance, but more cells encoded the relative distance. And, as in the duration discrimination task, many cells encoded conjunctions of stimulus features with relative distance.

If the dorsal PF cortex plays a critical role in discriminating distances, monkeys with lesions in that area should be impaired at a task in which they must report distance. Mishkin et al. (1977) taught monkeys to move a lever two different distances and then to report the distance by choosing between two stimuli. Monkeys with dorsal PF cortex lesions performed this task poorly. This result might reflect a poor judgement about movement distance, but it might also result from a deficit in judging the duration of movement, or both.

Conjunctions

We have said that cells in the dorsal PF cortex represent durations and distances, and in a previous section we mentioned a study in which it was reported that many PF cells encode order (Ninokura et al. 2003; Genovesio et al. 2009). These results should not be surprising given that the dorsal PF cortex receives a projection from the posterior parietal cortex, and cells there encode the same features (Tudusciuc & Nieder 2007; Bueti & Walsh 2009).

Cells in the PF cortex, however, differ from those in the posterior parietal cortex in an important way. As just mentioned, many cells in the dorsal PF cortex encode conjunctions of features. Cells in the posterior parietal cortex encode durations, but cells in the mid-lateral PF cortex in addition encode the conjunction of stimulus colour and duration, for example. In the study by Genovesio et al. (2009), the monkeys needed to report something about the conjunction of colour and duration, but they did not need to report anything about stimulus order, such as whether the first or second stimulus had lasted longer. Nevertheless, many neurons in the mid-lateral PF cortex encoded the conjunction of relative duration and stimulus order.

Similarly, in the subsequent study by the same authors (Genovesio et al. 2011) the monkeys had to report something about the conjunction of stimulus colour and relative distance but did not have to report information about order. Yet, many cells encoded both kinds of conjunctions. A smaller number of cells encoded whether the stimulus above or below the reference point had been farther away. These findings suggest that temporal order plays an especially important role the activity of cells in the mid-lateral PF cortex.

Figure 6.14 shows the signal encoding order-based conjunctions in the two tasks relative to the signal encoding the goal. The timing suggests that order-based conjunctions play an intermediary role in the generation of the goal. Later, many cells encode the reaching movement: the action that achieves the goal.

Order-duration, order-distance, and place-distance conjunctions are not the only kinds of integration observed in the mid-lateral PF cortex. Table 6.1 lists some of the conjunctive representations that occur in its neurons in other tasks. For example, Hoshi and Tanji (2004) showed monkeys two cues in a sequence, one telling them to reach to a goal on the left or right, the other telling them to use the left or right arm. The activity of cells recorded in the ventral part of the mid-lateral PF cortex tended to reflect spatial aspects of the cue, whereas cells recorded more dorsally tended to reflect the arm–goal conjunctions.

The dorsal PF cortex thus appears to be a summing point for signals of many kinds that lead to the generation of goals. It serves this function because of its connections: inputs from the posterior parietal cortex deliver spatial, temporal, and order contexts, inputs from the orbital PF cortex provide outcome information, and intrinsic connections of the PF cortex provide signals of other kinds.

Figure 6.15 provides an example of these kinds of interactions. Tsujimoto et al. (2011a) studied the relationship between neural signals that encode abstract strategies and those

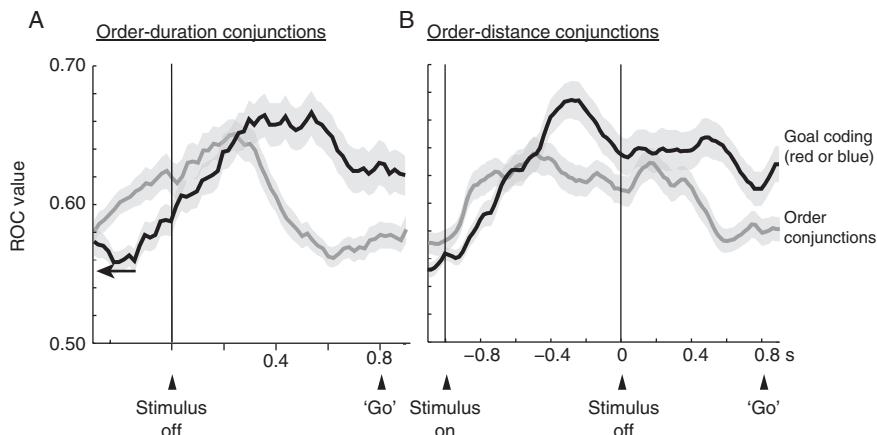


Fig. 6.14 Activity in the dorsal PF cortex encoding conjunctions. (A) Population activity for cells encoding the conjunction of order and relative duration (grey line). These cells encoded whether the first or second of two stimuli had lasted longer on a given trial. Shading: SEM. The ordinate shows the receiver operating characteristic (ROC) averaged over the individual cells, which indicates the average ability of each cell to encode a given order–duration conjunction. The arrow marks the chance-level ROC value. (B) Order-distance conjunctions in the same cortical areas (grey line). In the format of (A). The black line in both plots shows activity that encoded the goal, either the red or blue stimulus. (A) modified from Genovesio A, Tsujimoto S, Wise SP. Feature- and order-based timing representations in the frontal cortex. *Neuron* 63(2):254–66, © 2009, with permission from Elsevier. (B) modified from Genovesio A, Tsujimoto S, Wise SP. Prefrontal cortex activity during the discrimination of relative distance. *Journal of Neuroscience* 31:3968–80, © Society for Neuroscience, 2011, with permission.

Table 6.1 Conjunctive coding in the dorsal PF cortex

Conjunction	Source
Stimulus features and action	Kim and Shadlen (1999)
Stimulus identity and location	Rao et al. (1997)
Conjunctions of stimulus features	Roy et al. (2010)
Rules and action	Wallis and Miller (2003a)
Action and outcome (future reward quantity)	Wallis and Miller (2003b)
Action and outcomes (reward or nonreward)	Tsujimoto et al. (2009)
Stimulus features, strategies, and goals	Genovesio et al. (2005)
Outcome (reward or nonreward) and time	Tsujimoto and Sawaguchi (2005)
Action and guidance (memory or vision)	Tsujimoto and Sawaguchi (2004a)
Relative duration and order	Genovesio et al. (2009)
Relative distance and order	Genovesio et al. (2011)
Relative distance and location	Genovesio et al. (2011)

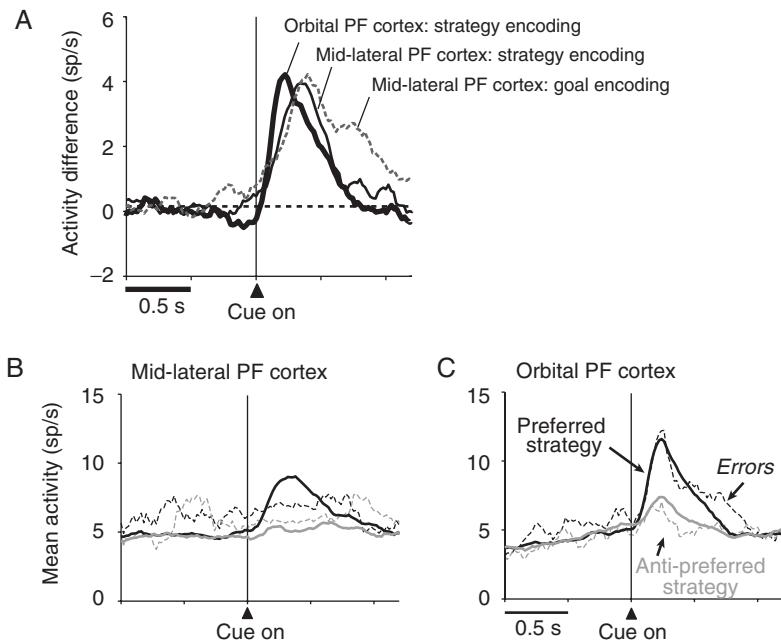


Fig. 6.15 The timing of strategy signals in mid-lateral and orbital PF cortex. (A) Strategy-coding signals from cell populations in the orbital and mid-lateral PF cortex and the goal signal from the mid-lateral PF cortex population. (B) Activity on correct versus error trials for the mid-lateral PF cortex. Solid lines: mean activity on correct trials; dashed lines: mean activity on error trials. Black lines: preferred strategy; grey lines, alternative (anti-preferred) strategy. The activity depicted by dashed lines did not differ significantly for preferred versus anti-preferred strategies. (C) Activity on correct versus error trials for the orbital PF cortex, in the format of (B). The orbital PF cortex has the same strategy signal on correct and error trials. Modified from Tsujimoto S, Genovesio A, Wise SP. Comparison of strategy signals in the dorsolateral and orbital prefrontal cortex. *Journal of Neuroscience* 31:4583–92, © Society for Neuroscience, 2011, with permission.

that encode the goals selected on the basis of those strategies. Chapter 3 explains this task, and we mention it earlier in this chapter, as well: an oriented bar or a coloured square cued monkeys to either stay with a previous goal or shift from it. White squares to the left and right of the fixation point served as potential goals.

Tsujimoto et al. found that cells in the orbital PF cortex encode the strategy earlier than those in the mid-lateral PF cortex (Figure 6.15A), in accord with OFC's connections with the inferior temporal cortex. When the strategy signal developed in the mid-lateral PF cortex, a goal signal appeared there, as well, a property that the OFC did not share.

The mid-lateral and orbital PF cortex differ in another way, as well. Strategy-encoding cells in the mid-lateral PF cortex show this signal weakly, if at all, on error trials (Figure 6.15B). But cells in the OFC did encode the correct strategy on error trials (Figure 6.15C). Taken together, these results suggest that the OFC provides a strategy signal to the dorsal PF cortex, which on correct trials generates a current goal based on that strategy and a memory of the

previous goal. Later, other cells in the orbital PF cortex encode the chosen goal at feedback time, irrespective of whether the choice was correct.

In addition to the examples of conjunctive coding in Table 6.1, which come from the dorsal PF cortex, additional ones appear in Table 8.2, where we consider the PF cortex as a whole.

Summary

Because of its connections with the posterior parietal cortex, the literature has tended to emphasize the role of the mid-lateral PF cortex in processing information about locations in space. However, posterior parietal cells also encode time intervals, temporal and spatial order, quantity, size, speed, length, and distance information, among other metrics. Thus its connections with the posterior parietal cortex enable the mid-lateral PF cortex to encode many features of events in addition to their location. Through its parietal and other connections, the mid-lateral PF cortex encodes conjunctions of previous choices in a series with their outcome, conjunctions of order and relative duration, and conjunctions of order and relative distance.

Conclusions

How the dorsal PF cortex does what it does

This chapter explains how the functions of the dorsal PF cortex, in general, and the mid-lateral PF cortex, in particular, depend on their connections:

1. The connections of the mid-lateral PF cortex with the posterior parietal cortex provide information not only about the location of visual events, but also about their durations and order, among other metrics such as number and relative distance. These connections explain why the delayed response task, and others like it, depend critically on the mid-lateral PF cortex. Given a series of trials, the appropriate goal depends on the location of the most recent visual event, which determines the appropriate current goal. This interpretation also explains results from the *n*-back task. On the three-back task, for example, the appropriate choice depends on what item appeared in a series three events ago. Therefore, we suggest that the order information provided by the posterior parietal cortex to the mid-lateral PF cortex plays a critical role in tasks like the delayed response task.

As a result of its posterior parietal connections, the mid-lateral PF cortex lies at the end of the dorsal visual stream, a system that plays a key role in the selection and control of actions. Sustained activity occurs during delay periods throughout this system, for example in the premotor cortex (Wise 1985), the preSMA and SMA (Shima & Tanji 2000), and the posterior parietal cortex (Kalaska & Crummon 1995). Delay-period activity and activation also occurs in the mid-lateral PF cortex. Although we know that many cells in the mid-lateral PF cortex encode retrospective spatial memories (Genovesio et al. 2006b) and that they encode the cued location in antisaccade experiments (Funahashi et al. 1993b), imaging results show that activations for prospective coding predominate over those for retrospective coding in this area.

2. The mid-lateral PF cortex has dense connections with the OFC (Barbas & Pandya 1989), and thus has access to information about outcomes in relation to current needs.
3. Through its connections with premotor areas, the dorsal PF cortex can promote the achievement of goals. These connections go to premotor areas that are specialized for the control of hand and arm movements, as opposed to foot and leg movements. This specialization suggests that the dorsal PF cortex generates goals primarily for reaching movements and for manipulation.
4. We also propose that the dorsal PF cortex generates an ordered series of goals, as required for planning a sequence, and its connections with the premotor areas enable the achievement of sequential goals. In support of this idea, some cells in the preSMA encode the rank-order of the movements in a sequence (Shima & Tanji 2000) and others code for the second movement while the monkey waits to initiate the first (Nakajima et al. 2009).
5. Many cells in the both the mid-lateral PF cortex (area 46) and the dorsomedial PF cortex (lateral area 9) encode conjunctions among features such as order, duration, colour, shape, and outcomes, and inputs from the posterior parietal cortex, orbital and ventral PF cortex, preSMA, perirhinal cortex, and other areas provide much of this information. We argue in Chapter 8 that this high level of integration results from the fact that the PF cortex lies at the top of three processing hierarchies, one for context, another for goals, and one for outcomes.

This chapter emphasizes the delayed response task because of its importance in the literature. More than 75 years ago, Jacobsen found that monkeys (Jacobsen 1936) and chimpanzees (Jacobsen 1935) with PF cortex lesions suffered profound impairments on a task of this kind. In the 1980s, Goldman-Rakic (1987) put forward the working memory theory of the PF cortex, largely on the basis of results from delayed response tasks and related ones. She argued that the mid-lateral PF cortex (area 46) plays a necessary and specific role in retrospective spatial working memory (Goldman-Rakic 1998). Chapter 10 takes up a general discussion of this theory, here we focus on its connectional aspects.

In accord with the ideas about dorsal- and ventral-stream function that were prevalent at the time (Ungerleider & Mishkin 1982), Goldman-Rakic emphasized the spatial inputs that the posterior parietal cortex provides to the PF cortex (Wilson et al. 1993). We, too, stress the importance of these connections but differ in our interpretation of what they provide to the PF cortex. We view the posterior parietal cortex as functioning in the selection and control of visually guided action (Shadmehr & Wise 2005; Milner & Goodale 2007). This view changes our understanding of what the posterior parietal cortex provides to the mid-lateral PF cortex (Rushworth 2000). For example, imaging activations occur there when people remember letters or shapes (Rushworth & Owen 1998). One might try to incorporate them into the working memory theory by expanding the role of the mid-lateral PF cortex to nonspatial, as well as spatial, working memory. But the more important factor is that these activations occurred in *n*-back tasks, which requires subjects to remember the order in which the items appear (Nystrom et al. 2000). So these

observations do, indeed, show that the function of the mid-lateral PF cortex extends beyond spatial analysis, but they probably reflect the need to encode order rather than anything to do with working memory per se.

Proposal

We can now offer a proposal concerning the function of the dorsal PF cortex, with the proviso that it mainly focuses on the mid-lateral PF cortex (area 46). It follows in brief and somewhat expanded form:

In brief:

The dorsal PF cortex generates goals that are appropriate for the current context and desired outcome, where recent events specify that context, and it prospectively encodes these goals until an attempt can be made to achieve them.

Expanded:

The dorsal PF cortex generates goals based on a current context that can include the location, duration, distance, number, size, speed, and order of recent events, especially visual events. It uses these features, such as spatial and temporal order, to generate both concrete and abstract goals, as well as sequences of such goals. When necessary, it prospectively encodes these goals until an attempt can be made to achieve them and in this way defeats interference from irrelevant events.

Why other areas cannot do what the dorsal PF cortex does

We have argued that the posterior parietal cortex provides the key inputs to the mid-lateral PF cortex. But if this was all there was to the matter, then lesions of the posterior parietal cortex should have the same effect as lesions of the mid-lateral PF cortex. It has been known for a long time that they do not. As Chapter 1 mentions, lesions of the posterior parietal cortex do not lead to an impairment on either the delayed response (Alexander & Fuster 1973) or delayed alternation (Ettlinger et al. 1966) tasks. As one consequence of these findings, we can conclude that the cells in the posterior parietal cortex with delay-period activity (Kalaska & Crammond, 1995; Snyder et al. 2000) do not play a necessary role in these tasks.

Given that the cell activity provides little guidance, we turn to anatomy to understand why the mid-lateral PF cortex plays a necessary role in the delayed response task, and related ones, whereas the posterior parietal cortex does not. We propose that differences in their connections explain these findings. For example, the posterior parietal cortex lacks the specific outcome information that the mid-lateral PF cortex receives from the orbital PF cortex. Chapter 4 explains that information about specific outcomes arrives first in the granular OFC, with a dominance of colour, shape, and texture vision. Through the intrinsic connections of the PF cortex, it can shortly thereafter arrive in the mid-lateral PF cortex, where it becomes integrated with information about goals. The mid-lateral PF cortex thus receives evidence about event order, along with the outcome associated with a potential goal and its current value. The posterior parietal cortex has the

former information, but only the mid-lateral PF cortex has all of the information needed to generate goals based on a current context *and* the predicted outcome.

Contribution to foraging choices

Chapter 2 explains that the dorsal PF cortex appeared during the evolution of anthropoid primates (see also Preuss 2011). If so, then we need to understand what advantage it conferred. The key may lie in visually based foraging strategies. Earlier, we reviewed evidence from the 25-door search task, which showed that monkeys with lesions of the mid-lateral and post-lateral PF cortex search for unseen peanuts in a disorganized way (Passingham 1985a). Normal monkeys search in an orderly sequence whether they can see the targets (Desrochers et al. 2010) or not (Taffe & Taffe 2011). Thus monkeys with dorsal PF cortex lesions seem to forage less efficiently than normal monkeys. The 25-door search task requires a ‘win-shift’ strategy, as does the delayed alternation task. An optimized sequence allows normal monkeys to implement this strategy effectively.

Of course, all animals need to optimize foraging by moving from one patch to another when the first patch has become exhausted (Plank & James 2008). But the 25-door search task does not involve moving from one place to another by locomotion. The anthropoid way of optimizing foraging places emphasis on reaching for targets, and in particular doing so on the basis of visual events. The advantage of efficient sequences of reaching movements might relate to the competition that individuals face when foraging in groups. This chapter implicates the mid-lateral PF cortex in both use of visual events to choose goals and the generation of efficient sequences of goals. It seems to enable anthropoid primates to know that the visual events of the recent past, including their order, timing, and locations, tell them what to do next and what to do after that. The same capacity, of course, allows them to change their foraging plans as new events transpire.

Chapter 2 also advances the idea that anthropoid primates evolved the dorsal PF cortex in the face of severe problems with resource volatility. In the wild, anthropoids predict food availability based on synchrony among individuals of the same tree species, elapsed time, and weather events such as prolonged heat. These predictions depend on the conjunction of object representations—of trees or fruits, for example—with the order and timing of events. The dorsal PF cortex represents conjunctions of these kinds, and it plays a necessary role in recognizing that the order of prior events has direct relevance to the choice of current goals, either through order coding or rule coding. The durations and order of events also inform the planning of goal sequences, as do the intervals between events, their number, locations, and relative distances.

This chapter proposes that one newly evolved part of the anthropoid PF cortex, the dorsal PF cortex, generates goals based on a current context provided in large part by its connections with the posterior parietal cortex. We suggest that its function reflects one kind of adaptation to diurnal foraging: efficient planning of current and future goals through the use of order, timing, and distance information. Another part of the granular PF cortex appeared at about the same time: the ventral PF cortex. The next chapter explores the kinds of contexts that it uses to generate goals and the connections that allow it to do so.

Chapter 7

Ventral prefrontal cortex: generating goals based on visual and auditory contexts

Overview

The ventral PF cortex generates goals based on visual and acoustic cues, which we call signs, and its connections explain why it alone can do so. The ventral PF cortex has connections with visual areas in the inferior temporal cortex and auditory areas in the superior temporal cortex, as well as with other PF areas. Its connections with temporal cortex provide visual and auditory signs, which establish a current behavioural context. The orbital PF cortex provides the link between choices and outcomes, which can sometimes be learned on the basis of a single event (Chapter 4). In many tasks, the ventral PF cortex generates goals in terms of concrete objects and places. In tasks involving abstract rules and strategies, however, the ventral PF cortex can generate sets or classes of goals to choose or to avoid. Given that the ventral PF cortex evolved in anthropoid primates (Chapter 2), we propose that it provides an advantage in using visual signs, integrated with information about sounds, to guide foraging choices at both close and far range.

Introduction

As Chapter 2 points out, people often describe primates as ‘visual animals’. The reason is that the fovea evolved in early haplorhines and trichromatic vision evolved in anthropoids. These advances enabled these animals and their descendants to discern minute differences in location, colour, shape, visual texture, glossiness, and translucence. This chapter reviews evidence that anthropoids use these visual features to provide cues about foraging opportunities, which we call *signs*. As Chapter 2 explains, by signs we mean non-spatial sights and sounds that serve as cues but do not necessarily correspond to whole objects.

Evolution has devised many ways to gain an edge in foraging. Some mammals have exploited their niche by elaborating body parts to exploit resources. The long noses of elephants allow them to forage in a way that other mammals cannot; the long necks of the



Fig. 7.1 The ventral PF cortex in macaque monkeys (left) and humans (right). Format as in Figure 1.2.

giraffes likewise provide unique foraging opportunities. We propose that anthropoids have instead elaborated certain brain structures, including the ventral PF cortex.

The previous chapter explains that the dorsal PF cortex generates the goal that is appropriate for the current context as specified by recent events, especially visual events. It explained the importance of the order, location, and timing of visual cues, among other features, stressing connections with the posterior parietal cortex. The ventral PF cortex has connections with the inferior and superior temporal cortex. As a result, visible or audible signs also specify a current context, which anthropoids can use either alone or in conjunction with the contexts determined by order, location, and timing.

Areas

In macaque monkeys, the ventral PF cortex includes the lateral convexity of the hemisphere ventral to the principal sulcus (Figure 7.1). In humans, the homologous areas lie in the inferior frontal gyrus. In both, the ventral PF cortex extends around the lateral extreme of the hemisphere as far as the lateral orbital sulcus.

The term 12/47, devised by Petrides and Pandya, reflects their opinion that area 47 in humans is homologous with area 12 in monkeys (Petrides & Pandya 2002b). In terms of cytoarchitectonic areas, ventral PF cortex includes area 45 and area 12/47 in macaque monkeys (see Figure 1.2). In humans, the ventral PF cortex includes areas 45 and 47.

Connections

Figure 7.2 shows the corticocortical connections of the ventral PF cortex. Several features stand out:

1. As already mentioned, the ventral PF cortex connects strongly with the temporal lobe. Ventral PF cortex has reciprocal connections with the inferior temporal cortex

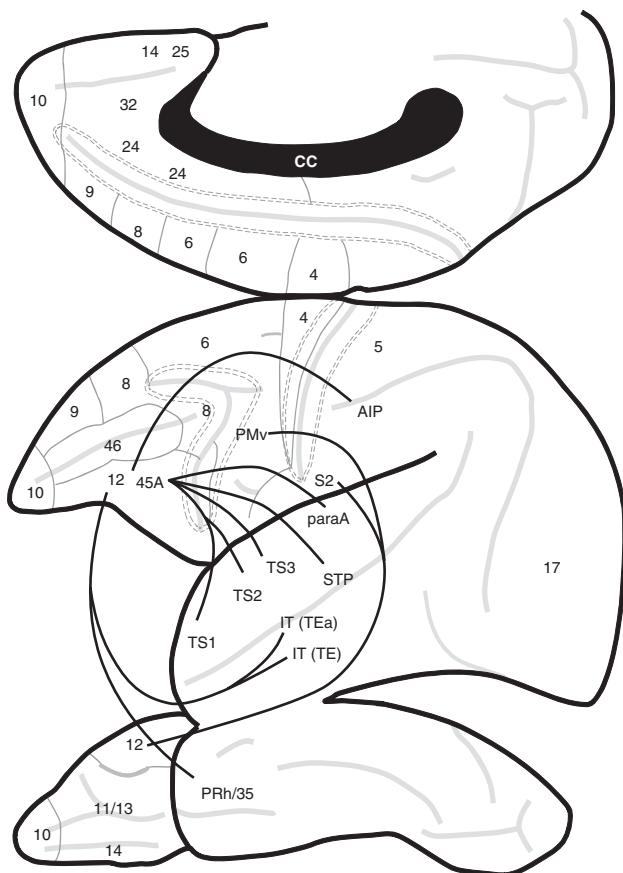


Fig. 7.2 Selected connections of the ventral PF cortex. Figures 1.4 and 1.5 give the names of sulci and areas. Lines connect some of the areas that have direct axonal connections with the ventral PF cortex, assumed to be reciprocal unless otherwise stated.

(Ungerleider et al. 1989; Webster et al. 1994) and the superior temporal cortex (Seltzer et al. 1996; Petrides & Pandya 2002b). It also has connections with the perirhinal cortex (Suzuki & Amaral 1994; Saleem et al. 2008), although not as many.

These connections have two implications. First, the ventral PF receives information about signals or signs that specify a behavioural context. The inferior temporal cortex plays a crucial role in the discrimination of colour, form, and visual texture (Huxlin et al. 2000). The superior temporal cortex is involved in the recognition of sounds (Tian et al. 2001) and sequences of sounds (Micheyl et al. 2005), including the calls of other animals (Rauschecker et al. 1995).

Second, information arriving in the ventral PF cortex comes from high- and middle-order visual areas, not from low-order ones. By high-order vision, we refer to the extensive conjunction of an object's features, which the perirhinal cortex represents (Murray et al. 2007). By contrast, inferior temporal areas, such as area TE, construct

middle-level conjunctions that fall between the representation of whole objects and their elemental features (Murray et al. 2007). The most caudal visual areas construct yet lower-order conjunctions and some represent elemental features, but these areas do not project to the ventral PF cortex (Webster et al. 1994). In this respect, the connections of the ventral PF cortex differ from those of the caudal PF cortex (Chapter 5).

2. The ventral PF cortex also has interconnections with the complex set of regions near and including the second somatosensory area (S2) (Petrides & Pandya 2002b). Thus the ventral PF cortex receives multimodal inputs, from visual, auditory, and somatosensory cortex. The cortex in and around S2 contributes to the tactile discrimination of objects (Mishkin 1979), and the perirhinal cortex is critical for identifying objects by visual or tactile sensation (Goulet & Murray 2001; Murray et al. 2007).
3. The ventral PF cortex receives an input from the inferior parietal area PG (Petrides & Pandya 2002b). This connection might provide information about the location of objects. The ventral PF cortex also receives an input from the posterior parietal area AIP, which seems to play a role in using vision to calibrate the grasp when a monkey picks up an object (Fogassi et al. 2001).
4. The ventral PF cortex (area 12/47) has strong connections with the rostral part of the ventral premotor cortex. One recent report has called this part of the premotor cortex area F5a (Gerbella et al. 2011), and Chapter 2 mentions that this area appears to control both hand and mouth movements.
5. The ventral PF cortex also has connections with the amygdala. Some neuroanatomists have described these as extensive (Amaral & Price 1984; Stefanacci & Amaral 2002), but others have viewed them as sparse (Carmichael & Price 1995a; Price & Drevets 2010). Regardless, the connections with the amygdala probably provide updated valuations, as Chapters 3 and 4 explain, either directly to the ventral PF cortex or indirectly via the orbital PF cortex. Lesions that include either the inferior temporal cortex (Horel et al. 1975) or the amygdala (Horel et al. 1975; Aggleton & Passingham 1981) affect whether objects seem attractive or aversive, and both have connections with the ventral PF cortex.

Summary

The ventral PF cortex receives information about visual and auditory signs from the inferior and superior temporal cortex, and it can integrate these aspects of the current behavioural context with information about outcomes from either the amygdala or the orbital PF cortex (Barbas & Pandya 1989), or both.

Visual and auditory conditional tasks

Given its connections with the temporal lobe, the ventral PF cortex can use information about the visual and auditory context to generate goals. Laboratory experiments can test this ability by using conditional tasks. These tasks involve arbitrary mappings between

contexts and the appropriate goal. So, for example, monkeys might learn that they should choose object 1 after cue A appears, but that they should choose object 2 after cue B appears.

When a visual context maps to a visual goal, the task is called either conditional visual–visual learning or paired-associate learning. When a visual context maps to a spatial context or directly to an action, it usually goes by the name conditional visuospatial learning, conditional visuomotor learning, or conditional motor learning. We use conditional visuomotor learning throughout this book.

The ventral PF cortex receives at least some of its information about the visual world via the uncinate fascicle. This fibre pathway connects cells in the inferior temporal cortex and the ventral PF cortex (Ungerleider et al. 1989). Cutting this pathway causes the monkeys to learn conditional visual–visual associations more slowly than normal (Eacott & Gaffan 1992; Gutnikov et al. 1997).

One can also teach monkeys a conditional auditory–visual task. Gaffan and Harrison (1991) taught monkeys to choose among six different visual stimuli, each instructed by one of six tones. They then disconnected the PF cortex from the superior temporal cortex by making a PF cortex lesion in one hemisphere and a superior temporal cortex lesion in the other. They cut the connections between the two cerebral hemispheres to complete the disconnection. Afterwards, the monkeys could not perform above chance level.

Once monkeys have learned tasks of this kind, one can find cell activity in the temporal lobe that reflects the learned associations. For example, Miyashita and his colleagues presented monkeys with a series of complex colour-and-shape stimuli and taught them arbitrary associations between pairs of these stimuli (Sakai & Miyashita 1991; Naya et al. 1996). After the animals had learned the pairs, cells in the inferior temporal cortex encoded the associations, and Miyashita and his colleagues called these pair-coding cells. Pair-coding cells occur prominently in the perirhinal cortex and rostral inferior temporal cortex and less frequently in the more caudal inferior temporal areas (Naya et al. 1996, 2001).

To show that these properties result from learning, Messinger et al. (2001) studied changes in cell activity in the perirhinal cortex and inferior temporal cortex while monkeys learned conditional visual–visual associations. They found that pair-coding properties developed during the initial stages of learning. Unfortunately, their monkeys only learned a little about the associations in the limited amount of time that Messinger et al. could study the activity of each cells.

Miyashita et al. (2004) provided evidence suggesting that the retrieval of these associations depends on the PF cortex. The experimenters cut the caudal part of the corpus callosum, while leaving commissural connections between the left and right PF cortex intact (Tomita et al. 1999). Presentation of a cue to the right temporal lobe nevertheless generated pair-coding activity for its goal stimulus in the left temporal lobe. These results imply that information about the cue stimulus goes from the right temporal lobe to the right PF cortex, then to the left PF cortex, and finally back to the left temporal lobe (Hasegawa et al. 1998; Tomita et al. 1999).

If so, then cell activity in the PF cortex should encode the associations between two pictures. Rainer et al. (1999) taught monkeys two tasks that used the same pictures as stimuli: one involved visual–visual mappings and the other involved the matching-to-sample rule. Activity early in the delay period typically encoded the cue, but activity later in the delay period most often encoded the goal. These results confirmed the existence of prospective coding in the PF cortex and localized at least a part of this function to the ventral PF cortex.

We say that these results confirmed prospective coding because Gaffan (1977) had already shown behaviourally that on a conditional visuomotor task monkeys encode the goal during the delay period. He manipulated the similarity of the colour of the instruction cues and the locations of goals and reasoned that if the monkeys retrospectively encode the instruction cue during the delay period, they should confuse similar cues, and they would reflect this confusion through erroneous choices. By contrast, if the monkeys prospectively encode the current goal, they would confuse nearby goal locations with each other. The findings supported prospective coding. Thus, during a delay period, monkeys predominantly hold goals in memory, rather than cues, and the results of Rainer et al. show that neurons in the ventral PF cortex encode goals prospectively.

Summary

The ventral PF cortex contributes to learning associations between cues and goals, including when auditory or visual cues guide a choice. During a delay period between the cue and goal attainment, monkeys prospectively encode the goal, and cells in the ventral PF cortex contribute to such prospective coding.

Visuospatial and visuomotor associations

In addition to objects and pictures, an action or location can serve as the goal in a conditional task. Thus, arbitrary visual cues can be associated either with hand movements (Bussey et al. 2001) or eye movements (Asaad et al. 1998). These mappings can be regarded either as conditional visuospatial associations or conditional visuomotor associations. Monkeys with combined lesions of the ventral and orbital PF lesions have severe impairments at learning associations of this sort (Bussey et al. 2001). And inactivation of the ventral PF cortex alone causes a similar effect (Wang et al. 2000).

Boussaoud and Wise (1993) recorded from the caudal part of the ventral PF cortex as monkeys performed various versions of the conditional visuomotor task. On different trials, the same stimulus could cue different hand movements, and different stimuli could cue the same movement. Only 16–18% of the PF cortex cells coded for the movement as opposed to features of the cue. By contrast, in the dorsal premotor cortex 51–64% of the cells encoded the movement. This difference points to the importance of visual signs in the function of the ventral PF cortex.

If the ventral PF cortex generates goals based on learned cue contexts, one might expect changes in activation during learning. So Toni et al. (2001) taught human subjects to move different fingers in response to different visual signs. In their experiment, the

subjects had to learn the arbitrary mappings by trial and error during scanning, with feedback being given at the end of each trial. In a control condition, arrows pointed to the appropriate finger and the subjects merely need perform as instructed, without learning any arbitrary mappings. The analysis looked for increases in activation over time for the learning compared with the control condition. Such increases occurred both in the inferior temporal cortex and in the ventral and dorsal PF cortex.

However, this experiment had two factors that distinguished the experimental and control conditions: learning and the use of arbitrary cues. So Boettiger and D'Esposito (2005) compared a condition in which the subjects learned cue-action associations by trial and error with a control condition in which the subjects had learned the associations before scanning. In their experiment, therefore, the two conditions differed only in that learning took place in the experimental but not the control condition. As in the experiment by Toni et al. (2001), learning-related changes in activation occurred in both the ventral and dorsal PF cortex.

Learning-related increases in activation could reflect something specific about mapping cues to action, but they could simply reflect an increase in attention to the outcome. The issue can be resolved by recording from cells in monkeys. Asaad et al. (1998) taught monkeys had to associate arbitrary cues with saccades to the left or right. Of the task-related cells in the dorsal and ventral PF cortex, 44% encoded the association between a specific cue and the associated saccade. Furthermore, as learning progressed, the activity that coded for the response occurred progressively earlier during the delay period. This change in activity seems unlikely to reflect attention to the outcome. The investigators could compare other combinations of cues and saccades that were associated with same outcome and thus rule out attentional and outcome-coding effects, at least for these cells.

In these experiments, the monkeys learned new cue-action associations as the investigators repeatedly changed the mappings between two stimuli and two goals. However, Cromer et al. (2011a) taught several new associations between cues and saccades using novel stimuli. The monkeys learned rapidly, and learning-related activity occurred in the PF cortex in parallel with the change in performance. And it occurred early in the trial, just as in the earlier experiment by Asaad et al. (1998).

Summary

The ventral PF cortex plays a key role in learning new associations between visual cues and spatial goals or actions. The evidence indicates a close correspondence between PF cortex activity and learning to generate goals based on cue contexts, and lesions that include the ventral PF cortex severely disrupt the learning of new cue-goal mappings. Chapter 8 revisits this topic.

Matching-to-sample tasks

Conditional tasks involve arbitrary associations between cues and goals. In this respect, these tasks differ from matching-to-sample tasks, in which the goal must match the sample.

The matching task imposes an identity rule for the relationship between cue and goal, as opposed to the arbitrary rule that monkeys must learn in conditional tasks. However, monkeys still need to learn to choose the object or picture that matches the sample, and in that sense they need to use a current cue as the context for choosing a goal.

In accord with this idea, the evidence shows that the ventral PF cortex plays a critical role in learning matching-to-sample tasks. Rushworth et al. (1997a) tested monkeys with ventral PF lesions on simultaneous matching for colours. This task uses the same rule as in the delayed matching-to-sample task. In the simultaneous version of the task, the sample remains visible as monkeys make a choice; in the no-delay version, also known as the zero-second delay version, the sample disappears at the same time as the choice stimuli appear.

In the experiment by Rushworth et al., removal of the ventral PF cortex led to a significant impairment in relearning the simultaneous matching-to-sample task (Figure 7.3). And the same result occurred after combined lesions of the ventral and orbital PF cortex (Bussey et al. 2001). And, for no-delay matching, disconnection of the ventral and orbital PF cortex from the inferior temporal cortex caused an impairment (Bussey et al. 2002).

We can devise three accounts for these results:

1. The monkeys might have a perceptual impairment. However, Bussey et al. (2001) tested their monkeys on a visual discrimination, and they learned it normally.

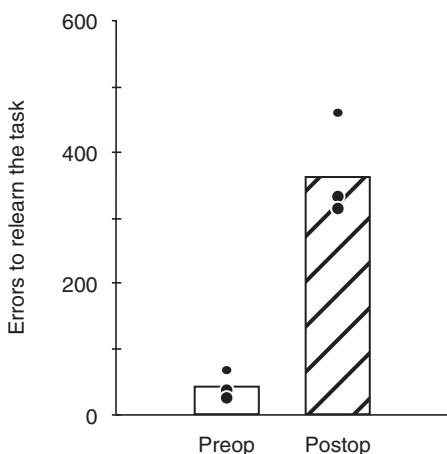


Fig. 7.3 Effect of ventral PF cortex lesions on the matching-to-sample task with simultaneous matching. In simultaneous matching, the sample remains visible at the time of the choice. Preoperative (preop) and postoperative (postop) performance for a group of monkeys, with the number of errors needed to relearn the task after a hiatus (white bar) and after the lesion (hatched bar) plotted on the ordinate. Filled circles show the performance of individual monkeys. Reproduced from Rushworth MF, Nixon PD, Eacott MJ, Passingham RE. Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience* 17:4829–38, © Society for Neuroscience, 1997, with permission.

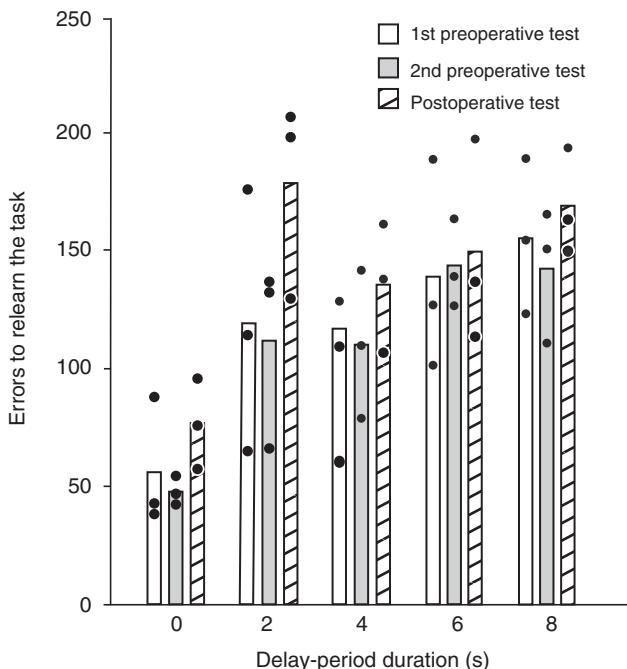


Fig. 7.4 Effect of ventral PF cortex lesion on the delayed matching-to-sample task, as a function of the delay interval. Format as in Figure 7.3 for two preoperative tests (white and grey bars) and one test after the lesion (hatched bar). Reproduced from Rushworth MF, Nixon PD, Eacott MJ, Passingham RE. Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience* 17:4829–38, © Society for Neuroscience, 1997, with permission.

2. The monkeys might try to remember the sample even though they do not need to, and therefore the results could reflect an impairment in working memory. However, this explanation cannot account for the results of the study by Rushworth et al. Their monkeys relearned the simultaneous matching task, and so Rushworth et al. could retest the lesioned monkeys with various delay periods between the sample and the choice stimuli. They made no more errors on delayed matching than before surgery (Figure 7.4). Kowalska et al. (1991) likewise found that once monkeys with ventral PF lesions had relearned the task rule, they performed normally on delayed nonmatching-to-sample task with long delays.

We know that delay-period activity occurs in the ventral and orbital PF cortex (Rosenkilde et al. 1981; Hoshi et al. 2000) and that delay-period activation occurs when human subjects perform the delayed matching-to-sample task (Rama & Courtney 2005; Schon et al. 2008). And we know that electrical stimulation of the orbital PF cortex during the delay period causes impairments on these tasks in monkeys (Sobotka et al. 2005). So we do not deny the existence of activity that some have interpreted in terms of retrospective working memory. And we do not deny that disrupting neural activity in these areas causes deficits on these tasks. However, the

results of Rushworth et al. demonstrate that the impairment on the simultaneous matching-to-sample task cannot be attributed to a problem with working memory: their lesioned monkeys performed normally at reasonably long delays once they had relearned the task rule.

3. Rejection of the first two accounts leaves a third possible explanation. After the lesion, the monkeys no longer knew the task rule, which they then had to relearn. In the matching-to-sample task, monkeys must use an identity rule: choose the object that matched the sample. Later in this chapter, we cite evidence for cell activity in the PF cortex that reflects the current task rule (Wallis et al. 2001). The impairment caused by electrical stimulation (Sobotka et al. 2005) could result from a failure to retain that rule.

Summary

To sum up the chapter to this point, the ventral PF cortex plays a critical role in the arbitrary mapping of visual or auditory cues to goals or actions. But its function extends beyond such associations. In the matching-to-sample task, the relationship between the cue and goal is not arbitrary. When monkeys learn the matching rule before a lesion of the ventral PF cortex, they show an impairment in applying that rule after the lesion. Monkeys with ventral PF lesions can, however, relearn the rule, and thereafter they demonstrate a normal working memory capacity. Thus their impairment on the matching-to-sample task occurs because the lesioned monkeys no longer know the rule immediately after the lesion.

Categorization

If the ventral PF cortex contributes to matching by colour or shape, and also to learning to associate different pictures, one might expect that it would also play a role in learning about categories of stimuli. Freedman et al. (2001, 2002) taught monkeys to distinguish drawings of cats and dogs, using a delayed matching-to-sample task. They produce a graded series of morphed drawings, and the monkeys learned the boundary between the category ‘cat’ and the category ‘dog’ (Figure 7.5). Cells can be found in the ventral PF cortex that encode one or the other category during the delay period (Figure 7.6).

The investigators went on to teach the monkeys new categories. This involved establishing new category boundaries, depicted by the grey vertical lines in Figure 7.4. Cells in the ventral PF cortex then code for one or another of the new categories (Figure 7.7). The importance of this finding lies in the arbitrary nature of the categories that the ventral PF cortex can learn; they do not depend entirely on the number of shared features.

Extending these studies, Cromer et al. (2010) taught monkeys two independent categories: cats versus dogs and sports cars versus sedans. In this situation, they found multi-tasking cells that encoded both categories. But when Roy et al. (2010) taught monkeys to switch between competing ways of categorizing cats and dogs, largely independent subpopulations encoded these mutually exclusive categories. This result resembles one that Chapter 6 mentions, in which largely independent subpopulations of cells in the dorsal

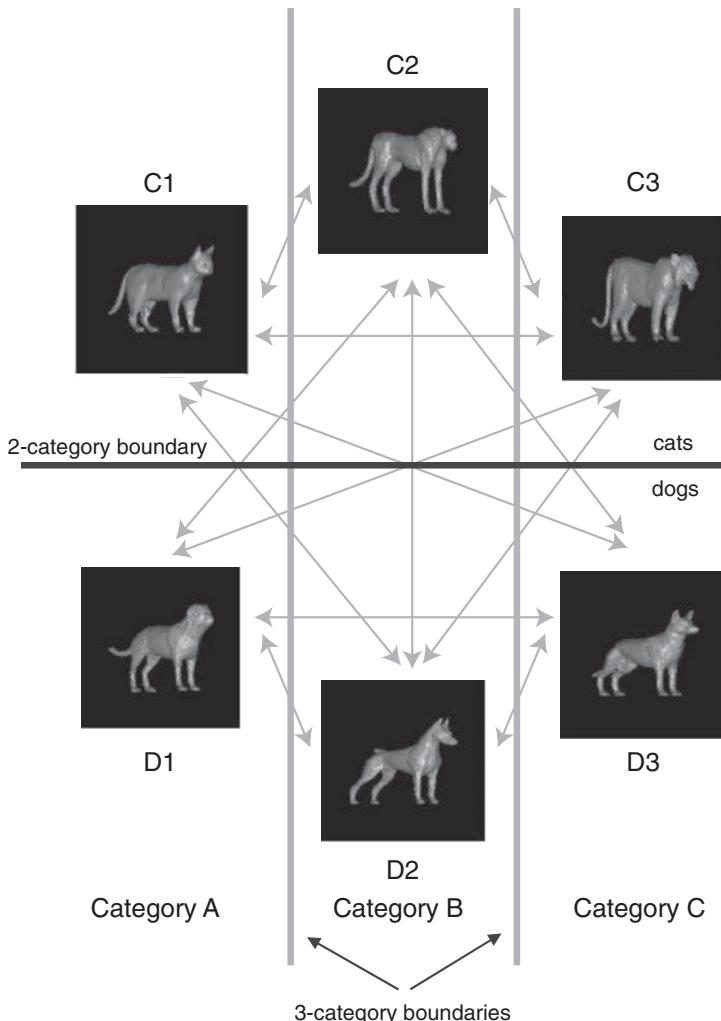


Fig. 7.5 Stimuli used in a categorization task. The experimenters constructed images comprising various proportions of two stimuli connected by the arrows. Drawings of three cats [C1 . . . C3] and three dogs [D1 . . . D3] and their morphed composites could be categorized as dogs versus cats, as separated by the black horizontal line. Alternatively, the same morphed stimuli could be categorized arbitrarily according to the three categories demarcated by the two grey vertical lines. Reproduced from Freedman DJ, Riesenhuber M, Poggio T, Miller EK. 2002. Visual categorization and the primate prefrontal cortex: neurophysiology and behavior. *Journal of Neurophysiology* 88:929–41, © The American Physiological Society, with permission.

PF cortex encoded current versus previous spatial goals, which are also mutually exclusive categories (Genovesio et al. 2006a).

These findings do not, of course, show that the ventral PF cortex cells are essential for the learning. The inferior temporal cortex could learn the categories and the PF cortex could retrieve the information from there. So Freedman et al. (2003) studied cells in both

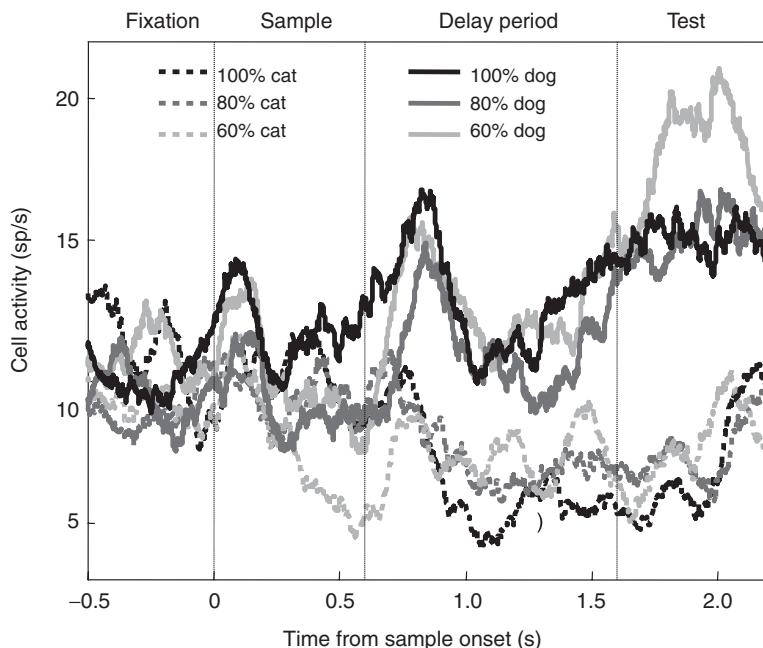


Fig. 7.6 A ventral PF cortex cell encoding the category 'dog'. Solid lines show the cell's activity for trials having a sample stimulus composed entirely (100%) or mainly (60% or 80%) of dog drawings. Dashed lines show activity for trials entirely or mainly consisting of cat drawings. During the delay period and the choice period (test), the cell had higher activity for samples in the category 'dog', as opposed to the category 'cat'. Reproduced from Freedman DJ, Riesenhuber M, Poggio T, Miller EK. 2002. Visual categorization and the primate prefrontal cortex: neurophysiology and behavior. *Journal of Neurophysiology* 88:929–41, © The American Physiological Society, with permission.

areas. Cells in the inferior temporal cortex did encode some information about categories, but, compared with cells in the PF cortex, their activity more often reflected the visual features of the stimuli (see also Meyers et al. 2008). This finding suggests that inferior temporal cortex represents visual features and feature conjunctions more strongly than categories and that the categorization learning occurs in the ventral PF cortex.

Cells in the inferior temporal cortex that represent the conjunction of features (denoted as AB) automatically encode the category of objects that have both features, as illustrated in Figure 4.3. So, for example, the archetype object with only features AB would be classified with objects with additional features, such as ABC, ABCD, and so on. The same principle applies to categorization within the PF cortex.

Accordingly, category coding and conjunctive feature coding have a close relationship, and the difference between the PF cortex and the inferior temporal cortex cannot be as simple as a distinction between category and feature coding. They differ, rather, in that the PF cortex learns abstractions from high- and middle-order conjunctions, whereas the

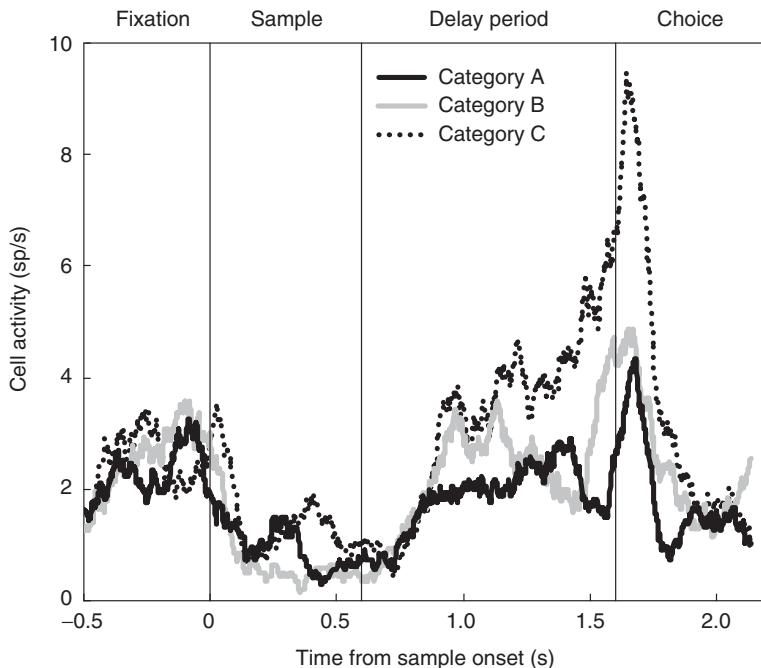


Fig. 7.7 A ventral PF cortex cell encoding arbitrary categories, demarcated by the vertical grey lines in Figure 7.5. This cell preferred morphed stimuli that fell to the right of the right-most grey vertical boundary, category C. Reproduced from Freedman DJ, Riesenhuber M, Poggio T, Miller EK. Visual categorization and the primate prefrontal cortex: neurophysiology and behavior. *Journal of Neurophysiology* 88:929–41, © 2002, The American Physiological Society, with permission.

inferior temporal cortex learns only middle-level conjunctions and does so less flexibly. The ventral PF cortex appears to learn, for example, that objects with features ABCD and ABCE can belong in category AB. But its cells can also learn that the same two objects belong in category AC. The inferior temporal cortex seems to learn the middle-level conjunctions AB and AC with less flexibility, based mainly on features rather than the additional factor of categorization.

Given that cell activity in both the PF cortex and inferior temporal cortex encodes categories, we might expect to find activation in both areas when human subjects classify pictures. DeGutis and D’Esposito (2009) taught people to classify faces into two categories, based on the height of the eyes and the length of the nose. The activations in the mid-lateral and ventral PF during the learning of these categories exceeded that for practised categories, and the activation in the inferior temporal gyrus increased only after the subject had practised a category.

These results may explain why, when subjects name or categorize pictures as animals or tools, activations do not generally occur in the PF cortex (Martin 2007). Instead,

activations occur in the temporal lobe for many kinds of visual categories, and in the premotor cortex for tools, presumably because tools can be handled. The PF cortex fails to show detectable activation because subjects have learned the categories of animals and tools during early education. For adults, the assignment of particular pictures to one or another class occurs automatically.

Of course, we do not mean to imply that adults lack the ability to learn new concepts and categories. One can teach an old dog new tricks. We take up the related topic of attentive versus automatic behaviour in Chapter 8. For the present purpose, it is enough to say that for well-practised categories, the relevant cognitive operations occur relatively automatically, especially in adults.

When pictures do not fall into a straightforward category, subjects have to devise new ones. In this case, the PF cortex becomes engaged. Thus, Degutis and D'Esposito (2007) found that when they compared the activations for easily categorized faces to those for more difficult ones, activation occurred in the mid-lateral and ventral PF only for the difficult categorization task.

We have argued that the PF cortex learns such categories by abstraction from middle- and high-order conjunctive representations. We have also argued that the ventral PF cortex can do this, whereas the inferior temporal cortex cannot do so as flexibly. And Cromer et al. (2011b) showed that cells in the premotor cortex lack information about categories, although some cell activity there reflects goal choices. So without denying the contribution of other areas to categorization and abstraction, the ventral PF cortex seems to play a key role in these functions.

Mimaminoto et al. (2010), however, tried to demonstrate that the PF cortex is not necessary even for learning new categories. They trained monkeys to perform a task in which stimulus A predicted one level of reward and stimulus B predicted another. With a little experience, the monkeys learn to generalize; that is, they treat a stimulus with some of the features of stimulus A as if it *was* stimulus A. Combined lesions of the dorsal and ventral PF cortex did not block this kind of generalization.

But the task used by Mimaminoto et al. did not require the monkey to compare items and construct arbitrary divisions among stimuli, as did the experiment by Freedman et al. Instead of learning arbitrary subdivisions that divide categories, a property that characterizes genuine categorization, the experiment of Mimaminoto et al. simply involved stimulus generalization, also known as feature generalization (Buckley & Sigala 2010). In stimulus generalization, if the animal has learned that a stimulus predicts something, it will also predict the same thing when presented with a stimulus sharing some of its features: the more shared features, the stronger the prediction. This primitive perceptual phenomenon occurs in all vertebrates and it has nothing to do with categorization.

By contrast, the experimental paradigm used by Freedman et al. (2002) did involve categorization. Their monkeys learned to divide the morphs into categories based on arbitrary divisions, not simply on the basis of some number of shared features. For example, when presented with the morph of dog that they have learned to be in the category 'dog', they could later learn to classify the same morph as 'cat'. The key distinction involves the learned and arbitrary subdivision of objects into categories, as in the experiment by

Freedman et al., as opposed to the automatic stimulus generalization in the experiment by Mimaminoto et al. We therefore accept the conclusions based on cell recordings, which indicate that the ventral PF cortex mediates flexible categorization of visual objects based on learning.

Summary

When monkeys learn to choose objects on the basis of the category to which they belong, cell activity in the PF cortex encodes that category. And the cells encode these categories as monkeys learn to categorize and re-categorize stimuli into any subsets that the experimenters choose to impose. Although monkeys with lesions that include the ventral PF cortex can still recognize stimuli as being similar, they do so via stimulus generalization, which is a phylogenetically old mechanism shared amongst all vertebrates, as distinct from genuine categorization. The ventral PF cortex plays its largest role when monkeys must choose a goal by applying a task rule to stimulus categories, such as the identity or matching rule.

Abstract rules

The study by Freedman et al. (2002) took advantage of the matching-to-sample rule to study categorization. This rule is abstract in that it can be applied to virtually any stimuli. Other abstract rules have the same property.

White and Wise (1999) found activity in caudal, ventral, postero-lateral, and dorsal PF cortex that encoded rules for guiding behaviour. Figure 7.8 shows the recording sites. White and Wise taught monkeys a conditional visuomotor rule and a visuospatial rule, with the colour of the central fixation spot specifying the rule for a block of trials.

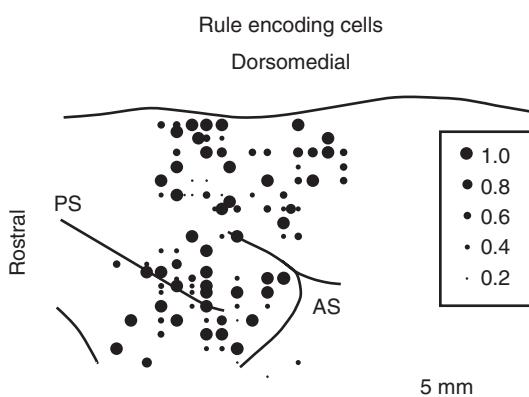


Fig. 7.8 Locations of rule-encoding cells. The diameter of each circle shows the proportion of cells recorded at each site that encoded one of two rules. One rule required the use of colour and shape stimuli to choose a goal; the other required using the cue's location to choose a goal. Abbreviations: AS, arcuate sulcus; PS, principal sulcus. With kind permission from Springer Science+Business Media. White IM, Wise SP. Rule-dependent neuronal activity in the prefrontal cortex, *Experimental Brain Research* 126:315–35 © 1999.

For the conditional visuomotor rule, the shape and colour of the cue told the monkey which goal to choose (among four or eight possible goals), and for the spatial rule the location of the cue did so. In order to receive a reward, the monkeys needed to make a saccade to the instructed goal and later press a bar when a light spot at that location dimmed.

Hoshi et al. (1998) carried out a similar study, but with reaching movements. They recorded from cells in the ventral PF cortex while the monkeys choose a reaching target based on stimulus shape (circle and triangles) or location. Many cells (36%) encoded reaching in terms of the two shapes, with a preference either for reaching to a circle or reaching to a triangle (feature–goal conjunctions). Many of these and other cells (34% overall) encoded reaching in terms of the rule, with a preference either for reaching based on stimulus location or reaching based on shape. These cells encoded rule–goal conjunctions, not movements per se.

As we mentioned earlier, Wallis et al. (2001) taught monkeys two abstract rules: delayed matching-to-sample and delayed nonmatching-to-sample. Then they presented novel stimuli at the start of each recording session. The application of an abstract rule does not depend on trial-and-error experience with the items used on any given trial. Of course, trial-and-error experience plays a key role during the learning of rules, but in this experiment the monkeys had learned the rules very well prior to recording the cell activity. In the experiment by Wallis et al., on each trial a sample picture appeared together with a cue telling the monkey which rule currently applied, matching or non-matching.

To ensure that any cell activity recorded after presentation of the cue reflected the rule rather than the sensory properties of the cue, Wallis et al. used two very different kinds of cues. Either a low-pitched tone or the delivery of juice instructed the monkey to apply the matching rule, and either a high-pitched tone or the absence of juice delivery instructed the nonmatching rule. On each trial, one of these instructions appeared at the same time as the sample picture, before the delay period. Usually, juice is regarded as a reward, and technically one can view it that way in these experiments. In the task devised by Wallis et al., however, the delivery of juice (or its absence) provided a cue for the current trial, just like the auditory signals that instructed the same rules.

During the delay period between the sample and the choice stimuli, some cells in the mid-lateral and ventral PF cortex encoded the matching rule (Figure 7.9) and others encoded the nonmatching rule. This result did not depend on either the stimulus items or the nature of the cue that instructed a rule (Wallis et al. 2001).

In a subsequent study, Muhammad et al. (2006) recorded from the inferior temporal cortex as monkeys performed the same task. They found only a few cells that encoded the rule. This result likely reflects the fact that the ventral PF cortex, but not the inferior temporal cortex, can integrate the cue context, the rule chosen by the monkey, and the outcome that results from choosing that rule. The inferior temporal cortex has much less direct and less specific information about outcomes than does the ventral PF cortex, which has extensive interconnections with the orbital PF cortex (Chapter 4).

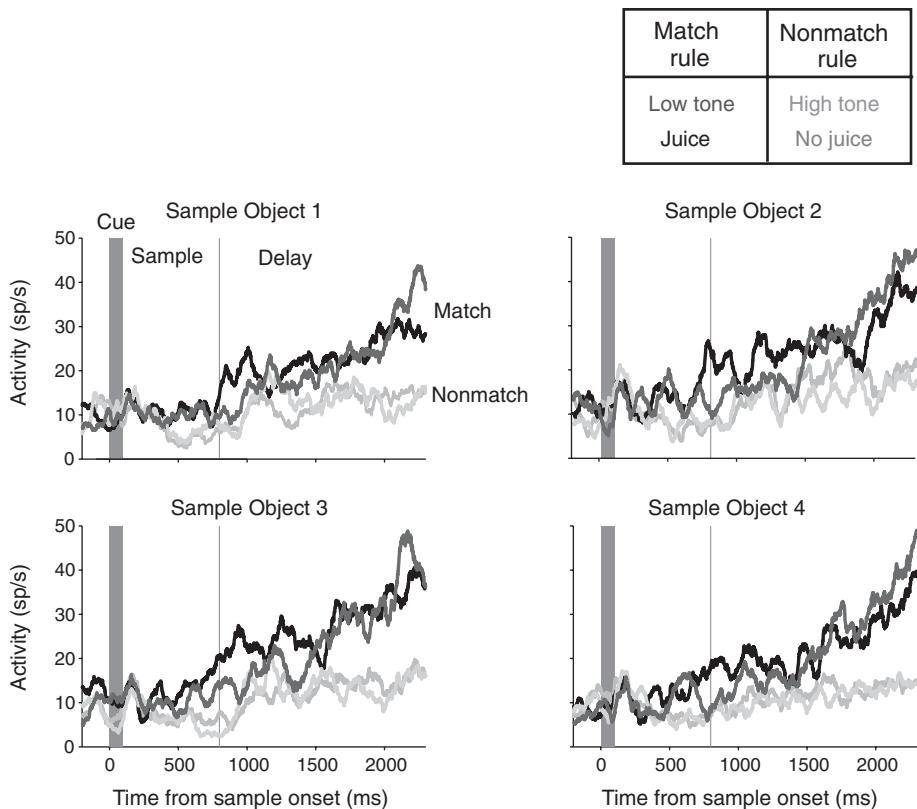


Fig. 7.9 Rule-encoding cell in the matching-to-sample and nonmatching-to-sample tasks.

Activity of a ventral PF cortex cells for four different sample stimuli [Object 1 . . . Object 4]. The inset at the upper right explains the four cues that instructed the monkeys to follow one of two rules: matching or nonmatching. Two cues, a low-pitched tone and the delivery of a juice reward, instructed the matching rule; two different cues, a high-pitched tone and the absence of juice delivery at the expected time, instructed the nonmatching rule. Dark lines: the cell's activity for the matching rule; light lines: activity for the nonmatching rule. Modified by permission from Macmillan Publishers Ltd. Wallis JD, Anderson KC, Miller EK. Single neurons in pre-frontal cortex encode abstract rules. *Nature* 411:953–6, © 1999.

Summary

Activity in the PF cortex reflects the current task rule, for example, whether the monkey should choose a goal that matches the sample or one that does not. This activity occurs during the delay period, after the presentation of the rule instruction. The rules apply to any stimuli, novel or familiar, and thus represent abstractions.

Changing rules

An abstract rule can establish a cognitive operation, such as matching or nonmatching, or it can designate the features of stimuli that are relevant for performing a task. Milner

(1963) adapted a task for human subjects in order to test specifically the ability to change rules based on stimulus features: the Wisconsin card sorting task. The subjects sort a series of cards into four separate piles according to coloured shapes on each card. On any one trial, the subject can sort a card according to the colour, shape, or number of the designs on that card.

In the standard version of the task, the subjects receive feedback after each trial, but only whether their choice had been correct or incorrect. At first, the subjects must learn to sort the cards by a given feature, for example, colour. The experimenter later changes the relevant feature, for example, to shape. The subject learns about the change in rule only from feedback, and so on through a series of rule changes.

Patients with large frontal lobectomies made what Milner (1963) called perseverative errors, and this interpretation has had a profound—but we believe misleading—impact on the literature. It implies that the patients have a specific problem with shifting from a previously successful rule. Yet these patients not only have an impairment in shifting from a current rule, they also have an impairment in learning new rules and staying with rules. Barcelo and Knight (2002), for example, found that patients with large frontal lesions make what they called random errors, as well as perseverative ones.

A random error involves making a mistake after a correct choice: a failure to *stay* with a recently successful rule. Chapter 4 explains that on object reversal tasks, monkeys with orbital PF lesions also make random errors in this sense (Rudebeck & Murray 2008). These errors reflect a failure to stay with a correct choice based on positive feedback. Chapter 3 shows the same kind of result for the medial PF cortex. And as we explain later, when monkeys learn conditional visuomotor tasks, ventral and orbital PF lesions cause the same impairments on ‘shift’ and ‘stay’ strategies (Bussey et al. 2001).

Accordingly, although we accept that frontal lobe lesions cause an impairment on the Wisconsin card sorting task, we reject the idea this deficit reflects a failure of behavioural inhibition or that it results from perseveration. Chapter 4 discusses some of the reasons for this conclusion, and Chapter 10 takes up the topic again in more detail.

Mansouri et al. (2006) devised a simplified version of the Wisconsin card sorting task for monkeys. The animals learned to match stimuli either on the basis of colour or on the basis of shape, with only reward or nonreward as feedback. Chapters 3, 4, and 6 mention results from this task, for lesions of the medial, orbital, and mid-lateral PF cortex, respectively (Buckley et al. 2009). The investigators also lesioned the ventral PF cortex, but the monkeys failed to relearn either matching rule after the surgery. They manage to get to about 60% correct, but no better. This finding adds to the evidence that the ventral PF cortex contributes critically to the learning and implementation of abstract rules.

Further evidence comes from the studies of Nakahara et al. (2002), who used imaging methods on monkeys and people as they matched by colour or shape and as they shifted between these rules. When the subjects shifted between rules, the activation lay in the caudal part of the ventral PF cortex in both monkeys and humans. The activation peak in humans was near the peak reported by Monchi et al. (2001) as subjects received negative feedback on the Wisconsin card sorting task. Monchi et al. specifically analysed the data for switch trials and found the peak activation in the ventral PF cortex (area 12/47).

The Wisconsin card sorting task has many variables, and so Hampshire and Owen (2006) used a different design that gives a purer measure of the ability to change rules. Their experiment compared extradimensional shifts with intradimensional shifts. The subjects first learn to discriminate between two complex stimuli, such as those depicted in Figure 7.10. Subjects, for example, learn to make a choice according to shape, while ignoring the foreground lines.

The subjects then learn an intradimensional shift, which requires them to discriminate between two novel compound stimuli, with the relevant stimulus dimension remaining the same: in our example, shape rather than foreground lines. Later, subjects learn an extradimensional shift, which requires them to discriminate between two different novel compound stimuli, but with the other dimension being relevant: in our example, the foreground lines. Baxter and Gaffan (2007) showed that shape is the salient feature for the intradimensional shift, and this means the subjects did not need to change the rule, whereas on an extradimensional shift they do need to switch from one rule to the other.

Hampshire and Owen (2006) contrasted the activation for extradimensional and intradimensional shifts and found greater activation in the caudal part of the ventral PF cortex for a task involving rule shifts, that is, the extradimensional shift task. As already mentioned, the peak occurred near the one Monchi et al. (2001) reported for the Wisconsin card sorting task.

As one would expect, patients with frontal lobectomies make more errors on extradimensional shifts than normal subjects, but have no impairments on intradimensional shifts (Owen et al. 1993).

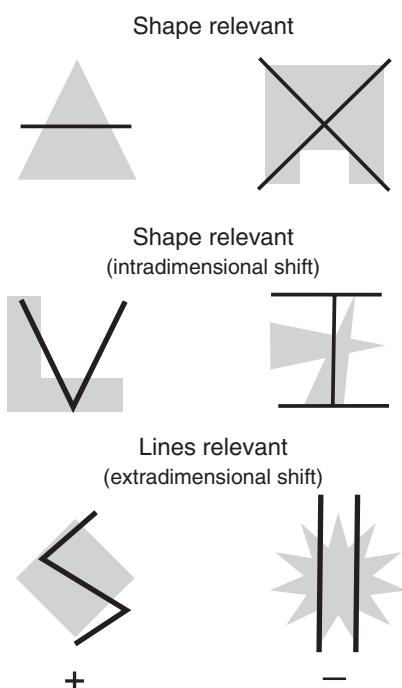


Fig. 7.10 Example stimuli for the extradimensional- and intradimensional shift tasks. Each horizontally arrayed pair of compound stimuli represents a choice. The correct, rewarded choice is noted at the bottom by the +, the incorrect choice by the -. Reproduced from Dias R, Robbins TW, Roberts AC. Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behavioural Neuroscience* 110:872–86, © 1996, American Psychological Association.

As yet, no one has made selective lesions in macaque monkeys with these tasks, but Dias et al. (1997) have done so in common marmosets (*Callithrix*). They compared the effects of lesions of the ventral PF convexity and the orbital PF cortex. The pattern of corticocortical connections suggests that the former area is homologous with ventral PF cortex (areas 12/47 and 45) in macaque monkeys (Roberts et al. 2007).

Marmoset monkeys with lesions of the ventral PF convexity could learn an extradimensional shift, but only slowly compared to normal marmosets (Dias et al. 1997). However, they performed normally on an intradimensional shift. This finding provides further support for a role of the ventral PF cortex in abstract rules that guide behaviour.

Summary

Monkeys with ventral PF lesions fail to relearn abstract rules, for example, to match by colour or shape. They also perform poorly at changing rules, for example, on extradimensional shift tasks and the Wisconsin card sorting task.

Abstract strategies

Previous sections mention abstract rules. By *rule* we mean an input–output algorithm that specifies the solution to a problem. We distinguish these from the *strategies* that monkeys can use when they try to solve a problem (see the Glossary for definitions). Rules say what one must do, whereas strategies say what one might do to solve a problem.

To illustrate what we mean by strategies, consider the conditional visuomotor task described earlier. As already mentioned, Bussey et al. (2001) trained monkeys on a series of conditional visuomotor problems. Each coloured shape mapped to one and only one of three or four spatial goals. The experimenters scored the first choice made when a new trial began, but also used a correction procedure after an error until the monkey got it right.

Before surgery, but after extensive experience in solving such problems, the monkeys learn new cue–goal mappings very quickly. But they learned something else, as well. They learned three abstract strategies: ‘repeat-stay’, ‘change-shift’, and ‘lose-shift’. According to the first strategy, if the cue repeats from the previous trial, the monkey should ‘stay’ with the same goal. According to the second strategy, if the cue changes from the previous trial, the monkey should ‘shift’ to an alternative goal. According to the third strategy, if the monkey made an error, it should ‘shift’ to a different goal.

Monkeys with ventral and orbital PF lesions lose the ability to apply all of these strategies after surgery (Bussey et al. 2001). We present more evidence on this point in Chapter 8 (Figure 8.6). Here we consider the mechanism for strategy implementation by appealing, once again, to the accumulator–racetrack model that Chapter 3 introduces. An accumulator network can implement the ‘change-shift’ strategy, for example, by integrating the ‘evidence’ for this strategy. When it reaches its threshold, this network could bias the activity of goal networks so that the previous goal cannot ‘win’ the ‘race’. In this way, a three-choice problem will have been converted into a two-choice problem, and errors will go down by ~17% as a result.

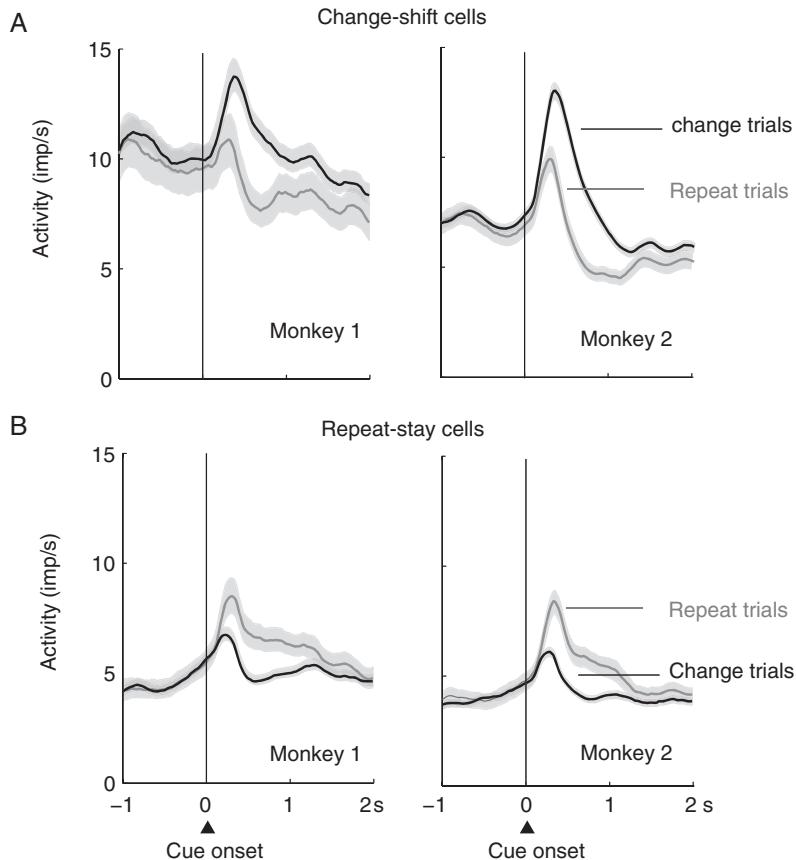


Fig. 7.11 Population coding for abstract strategies. (A) Average population activity for cells encoding the change-shift strategy for two monkeys (left and right). Black lines: activity on change trials, which were trials in which a change in cue from the previous trial indicated that the monkey should choose a different goal. Grey lines: activity on repeat trials, which were trials with the same cue as on the previous trial. Shading: SEM. (B) Population activity for cells encoding the repeat-stay strategy. Format as in (A). Reproduced from Genovesio A, Wise SP. The neurophysiology of abstract strategies. In *Rule Guided Behavior*, ed. SA Bunge, J Wallis, pp. 81–105, 2008, with permission from Oxford University Press.

Genovesio et al. (2005) recorded in the PF cortex in monkeys that had been trained to follow the ‘repeat-stay’ and ‘change-shift’ strategies. They found that many cells in dorsal PF cortex, including the mid-lateral PF cortex, encode either the ‘repeat-stay’ or ‘change-shift’ strategy (Figure 7.11). The strategy encoding does not simply reflect the change or repeat of the cue, because some cells specifically encode the spatial goal chosen on the basis of the stimulus. And, during error trials, strategy encoding becomes very weak or absent altogether in the dorsal PF cortex (Genovesio et al. 2008). Tsujimoto et al. (2011a) found cells in the orbital PF cortex that also encode these strategies, and they showed that cells in the orbital PF do so before cells in the mid-lateral PF cortex (Chapter 4).

Gaffan et al. (2002) devised a task to specifically assess the ability of monkeys to learn an abstract strategy that involved both staying with and shifting from goals. On their strategy task, the monkey learned to choose one object-like stimulus on the screen four times in a row, and then another stimulus just once. To perform each problem optimally, therefore, the monkey must classify one set of stimuli as persistent and another set as sporadic and choose each class of goal the appropriate number of times. Baxter et al. (2009) showed that lesions of ventral PF cortex cause a significant deficit on relearning this kind of strategy task. Lesions of the orbital PF cortex (Baxter et al. 2007) and the mid-lateral PF cortex (Baxter et al. 2008) have no such effect.

Summary

Lesions that include the ventral PF cortex prevent monkeys from using strategies that they learned spontaneously before the lesions, and they do not seem to relearn them afterwards. Abstract strategies help monkeys use what they have learned about solving similar problems to reduce errors when they face new problems, even though these strategies cannot eliminate errors entirely.

Conclusions

How the ventral PF cortex can do what it does

This chapter explains how the connections of the ventral PF cortex support its unique functions.

1. The ventral PF cortex generates goals based on visible signs. Along with the order, timing, and location of sensory events (Chapter 6), these signs establish an important part of a current behavioural context. The ventral PF cortex can perform its function because of its connections with the inferior temporal cortex and the perirhinal cortex, which represent objects and other conjunctions of visual features.
2. The generation of goals based on auditory signs depends on its connections with the superior temporal cortex. And it probably has a similar function for somatosensory stimuli based on connections with parietal areas.
3. The ventral PF cortex also receives information about outcomes via its connections with the orbital PF cortex, and about current needs both directly from connections with the amygdala and indirectly via the orbital PF cortex. It therefore can generate the appropriate goal both for the current context and the desired outcome, as assessed in terms of current biological needs.
4. Its connections with premotor areas probably account for its role in conditional visuomotor mappings, although the precise pathway remains uncertain; connections with the inferior temporal cortex mediate conditional visual–visual associations.
5. The ventral PF cortex receives convergent inputs concerning context, goal, and outcome through connections with the temporal cortex, prefrontal and premotor areas, and the orbital PF cortex, respectively. In the next chapter, we develop the idea that the PF cortex sits at the apex of processing hierarchies for contexts, goals, and

outcomes. Because of its status in these hierarchies, the ventral PF cortex not only can generate concrete goals, but also abstract ones such as sets, classes, or categories of goals; places and objects to avoid; and various combinations of concrete and abstract goals. The ‘change-shift’ strategy, for example, produces a set of potential goals through the avoidance of a place or action.

6. The ventral PF cortex not only can generate abstract goals, but it can also generate goals based on abstract rules and strategies. The signals that instruct rules and strategies probably depend on connections with the superior temporal cortex for tones (Wallis et al. 2001), the inferior temporal cortex for colour (Tsujimoto et al. 2010), and either the orbital PF cortex, amygdala, or dopaminergic neurons for outcomes. Abstract rules and strategies allow monkeys to apply what they have learned in similar situations to novel stimuli.
7. The cognitive operations mediated by the ventral PF cortex can also enhance representations in other cortical areas. Chapter 5 explains that the ventral PF cortex influences information processing in sensory areas of cortex through top–down attention. The connections of the ventral PF cortex with the inferior temporal and perirhinal cortex allow it to both mediate visual rules and strategies and to bias sensory processing toward relevant stimuli. Its connections with the caudal PF cortex also contribute to this role. Thus, if the task rule involves shape or colour, the connections of the ventral PF cortex with the inferior temporal cortex, both directly and indirectly via the caudal PF cortex, enable it to influence representations in the relevant area.

Proposal

These ideas lead us to the following proposal, first in brief form, then expanded a little.

In brief:

The ventral PF cortex generates the goal that is appropriate to the current context and desired outcome, as evaluated in terms of current needs. The goal can be either an object, location, or action and it can be either concrete or abstract.

Expanded:

The ventral PF cortex generates goals based on visual and acoustic signs that compose a current context. Goal generation also depends on a desired outcome, as evaluated in terms of current needs. In addition to concrete goals, such as objects and places, the ventral PF cortex generates abstract goals, such as a set, class, or category of goals to choose or to avoid. It also generates goals based on abstract rules and strategies. Through interconnections with the caudal PF cortex and with sensory areas, it biases the information it receives toward the features relevant to the current task.

Why other cortical areas cannot do what the ventral PF cortex does

We propose that the ventral PF cortex can perform these functions, whereas other brain areas cannot, and we do so for a simple reason: its connections. In conditional visuomotor

tasks, for example, monkeys must learn to associate a cue and an action with an outcome. We explained earlier how the ventral PF cortex gets the information needed to establish these conjunctions: cue, action, and outcome from temporal, premotor, and orbital cortex, respectively. Other parts of the cortex cannot get all of this information as directly. Some areas, such as the posterior parietal cortex, lack strong connections with the amygdala or the orbital PF cortex. Some, such as the superior and inferior temporal cortex, lack the kind of access to premotor areas that the ventral PF cortex has. And others, such as the premotor cortex, do not receive the inputs from temporal cortex that the ventral PF cortex gets.

Critics might object to some of these conclusions. The posterior parietal cortex, for example, has visual inputs and outputs to the premotor areas. And indeed cells can be recorded in the posterior parietal area LIP that encode whether the colour of a cue or its spatial location specifies the direction of the appropriate action (Toth & Assad 2002). Cells have also been reported in the posterior parietal cortex that encode shape (Janssen et al. 2008; Srivastava et al. 2009); so the separation between the dorsal and ventral visual streams is not as absolute as sometimes depicted. Furthermore, we say that the posterior parietal cortex does not receive much input from the orbital PF cortex, but this does not mean it lacks any information about outcomes. We know, for example, that cells in the posterior parietal cortex encode the magnitude or probability of reward (Platt & Glimcher 1999) and that they receive inputs from dopaminergic neurons in the midbrain. Critics of our conclusions could make similar arguments about the premotor cortex.

Despite these objections, we maintain that the posterior parietal cortex does not receive the kind of detailed information about the sight and taste of foods that the ventral PF cortex does, nor does the premotor cortex. Neither area has direct connections with the orbital PF cortex, which represents specific outcomes (Chapter 4), and there is only a sparse connection between the premotor cortex and the amygdala (Avendaño et al. 1983). It is for this reason that lesions of the superior or inferior parietal cortex have no effect on the relearning of conditional visuomotor tasks (Rushworth et al. 1997b).

As for the premotor cortex, it does, of course, cause an impairment in the conditional visuomotor task (Halsband & Passingham 1985; Petrides 1987). But whereas cells in the ventral PF cortex encode visual signs, the cells in the premotor cortex mainly encode the upcoming movement (di Pellegrino & Wise 1991). Thus the ventral PF cortex, and not the posterior parietal or the premotor cortex, is in a position to generate goals according to visual signs.

Contribution to foraging choices

The ventral PF cortex evolved in anthropoid primates as their brain and bodies expanded, after the evolution of the primate fovea and along with the development of trichromatic vision. The haplorhine ancestors of anthropoids adopted a diurnal foraging strategy that promoted the use of distant cues in making foraging choices. In the wild, visual and acoustic signs indicate the availability of resources. The exquisite, full-colour vision of anthropoid primates allows them to discern signs of foods or other resources at a distance, as well as the quality of foods and fluids in a local foraging patch. Their ventral PF

cortex also allows anthropoids to integrate this visual information with sounds from competitors and conspecifics that also serve as signs of resources. Chapter 2 explains, for example, that foraging choices of anthropoid monkeys often seem to depend on what they see or hear in trees, and their selection among items in their immediate locale depends heavily on subtle variations in the visual properties that distinguish among food items of the same type.

Chapters 3–7 explore the PF cortex region-by-region because its connections vary region-by-region. That exploration ends here. The remainder of the book deals with the PF cortex as a whole. In the next chapter, we suggest that it has a simple fundamental function.

Chapter 8

Prefrontal cortex as a whole: generating goals from current contexts and events

Overview

The granular PF cortex sits at the top of three information-processing hierarchies: one for current contexts, another for goals, and a third one for behavioural outcomes. As the apex of a context hierarchy, the PF cortex integrates cortical inputs for spatial and nonspatial vision, tactile and visceral sensation, audition, taste, and smell, along with inputs from the hippocampus. As the apex of a goal hierarchy, the PF cortex represents the goals of action, including sequences, sets, and categories of both concrete and abstract goals, and it can influence their achievement through connections with the premotor cortex. As the apex of an outcome hierarchy, it represents specific foods and fluids in all their sensory dimensions and, through connections with the amygdala, it updates their motivational valuation in terms of current biological needs. By integrating these three hierarchies, the anthropoid PF cortex can generate goals that are appropriate to the current context and current needs. As a specific adaptation to the foraging problems that anthropoid primates faced during their evolution, they can learn to generate goals on the basis of a single event and thus reduce the number of dangerous or unproductive foraging choices. Anthropoid primates solve new foraging problems more rapidly than their ancestors could because their newly evolved PF areas implement a fast, general-purpose learning system, which augments the ancestral reinforcement-learning mechanism that evolved early in the history of animals.

Introduction

The previous five chapters take the PF cortex apart, and the time has come to put it back together. Chapters 3 and 4 discuss the medial PF cortex and the orbital PF cortex, respectively. We argued, for example, that information about current biological needs reaches the orbital and medial PF cortex through connections with the amygdala and that the

hippocampus provides information to the medial PF cortex about navigation and other events involving actions. Chapter 5 interprets the function of the caudal PF cortex in terms of search and attention, effectuated through connections with both the dorsal and ventral visual streams. Chapter 6 proposes that information about space, time, and order reaches the dorsal PF cortex from the posterior parietal cortex and contributes to choices based on these contexts. And Chapter 7 says that information about visual and auditory signs reaches the ventral PF cortex from the temporal cortex and contributes to choices based on these other kinds of contexts.

This way of discussing the PF cortex could create the impression that it operates as five separate regions. But the PF cortex acts as a whole, and it can do so because its intrinsic connections allow it to integrate the information that arrives via different routes. Accordingly, the primate PF cortex can generate goals based on an overall prediction about outcome and an overall context. The contribution of the PF cortex goes beyond this kind of far-reaching integration, but the ability to bring information together in this way serves as one foundation for its fundamental function.

Because the PF cortex functions as a whole, we need a comprehensive theory, and Chapter 1 sets forth two requirements for such a theory: showing what the PF cortex does that other parts of the brain cannot do and explaining why its connections enable it to function in that way. We begin, as before, with connections.

Connections

Chapters 3–7 each have a section highlighting the connections of one part of the PF cortex. We summarize the overall pattern here.

Cortex and amygdala

1. The granular PF cortex receives information from visual, auditory, somatosensory, olfactory, gustatory, olfactory, and visceral cortex. The primate PF cortex thus has relatively direct inputs from distance receptors, such as those for vision and audition, along with inputs relaying specific behavioural outcomes, such as the taste, smell, sight, and feel of foods and fluids. As a result, the primate PF cortex has a robust, high-dimensional representation of specific behavioural outcomes, especially including their visual properties. It also has sophisticated representations of visual and auditory signs that can guide foraging or social choices. The visual signs reflect some of the evolutionary advances in primates, such as the fovea and trichromatic vision. The PF cortex of other mammals and other parts of the primate neocortex lack at least some of these properties.
2. The PF cortex also receives both direct and indirect inputs from the hippocampus and other parts of the hippocampal complex. The hippocampus, the subiculum, and the entorhinal cortex all have direct connections with the medial PF cortex. The hippocampus plays a role in navigation and in event memories, especially for events and objects as embedded in their spatial and temporal context. Like the PF cortex, the hippocampal complex receives inputs from all sensory modalities and has dense interconnections with the amygdala that convey some aspects of behavioural

outcomes. But whereas the PF cortex has direct outputs via the premotor areas, the hippocampus has less direct access to these areas, lacks the kind of intrinsic connections that the PF cortex has, and does not have the same kind of direct, specific outcome information that the PF cortex has (Chapter 4).

3. The amygdala has dense interconnections with many parts of the PF cortex (see Figure 3.3). Regions such as the posterior parietal cortex have few, if any, such connections. Some premotor areas have connections with the amygdala, but they are sparse (Avendaño et al. 1983). Connections of the PF cortex with the amygdala play a role in updating the motivational valuations of behavioural outcomes according to an animal's current state. So the PF cortex is in a position to represent updated valuations in a way that the posterior parietal and premotor cortex are not.
4. The PF cortex projects directly and indirectly to both the medial and lateral premotor areas and can thereby provide these areas with the goal of movements. The rostral part of the premotor cortex has extensive connections with the PF cortex, but caudal parts also get information from the PF cortex, albeit less directly. These connections, for the most part, exclude motor representations of the leg and foot. A specialization for forelimb as opposed to hindlimb representations has been shown for the rostral part of the dorsal premotor cortex (Tachibana et al. 2004), the ventral premotor cortex (He et al. 1993), the preSMA (Luppino et al. 1991), and the rostral cingulate motor area (He et al. 1995). As Chapter 2 explains, this forelimb bias reflects a hindlimb-dominated form of locomotion in primates, which freed the hands for other functions. Through its connections with the premotor areas, the PF cortex plays a preferential role in reach, grasp, and manipulation, as opposed to locomotion. These connections promote the achievement of goals such as grasping objects or reaching to places.
5. The PF cortex also has connections that control attentional and search functions, including eye movements, which correspond to overt attention (Chapter 5). For example, the caudal PF cortex has both direct projections to brainstem oculomotor nuclei and indirect ones via the superior colliculus and basal ganglia. Chapter 2 points out that most of the granular PF cortex in primates has strong corticotectal projections (Leichnetz et al. 1981). The PF cortex also sends projections to both the parietal and temporal lobes that mediate top-down attention for both the dorsal and ventral visual streams, and for the other sensory modalities, as well.
6. The various parts of the primate PF cortex have extensive connections with each other. These projections have been documented in detail elsewhere (Barbas 1988; Carmichael & Price 1995b; Barbas et al. 1999; Petrides & Pandya 1999, 2002a; Price 1999). Any input from outside the PF cortex can reach any part of the PF cortex in as few as two synaptic steps (Averbeck & Seo 2008). Not only does the PF cortex receive a vast array of inputs, but it can combine these inputs quickly regardless of where the information first arrives.

In addition to connections with other parts of the cortex and with the amygdala, the primate PF cortex has connections with the claustrum, basal ganglia, thalamus,

dopaminergic neurons in the midbrain, and the cerebellum. The next five sections take these up, in turn.

Clastrum

The claustrum has reciprocal connections with the PF cortex (Tanné-Gariepy et al. 2002) and also projects to it via the mediodorsal (MD) nucleus of the thalamus (Erickson et al. 2004). It has similar connections with the remainder of the cortex, as well. Projections from several cortical areas converge on a given patch of the claustrum, each of which connects to several parts of the frontal lobe, including the PF cortex (Tanné-Gariepy et al. 2002). This pattern of connections suggests that the claustrum may achieve a degree of integration. However, it appears to lack the extensive intrinsic connections that characterize the PF cortex.

Basal ganglia

Like most of the cerebral cortex, the PF cortex sends a heavy projection to the basal ganglia, targeting its input structure, the striatum. Despite a massive input from most, if not all, of the cerebral cortex, the output of the basal ganglia seems to focus on the frontal lobe, although some outputs go to the posterior parietal (Clower et al. 2005) and temporal cortex (Middleton & Strick 1996), as well. This organization suggests that the connections between the PF cortex and basal ganglia may also contribute to its role in integrating information.

However, the way it might contribute to this integration remains controversial. The basal ganglia lack the far-ranging intrinsic connections that could integrate information in its various parts. The prevailing view emphasizes a parallel assembly of cortex–basal ganglia loops, with minimal overlap (Alexander & Crutcher 1990; Nakano 2000). Figure 8.1 depicts some of these loops, including one premotor area (the SMA) and several PF areas. Middleton and Strick (1994, 2000) concluded that the loops involving the PF cortex are, by-and-large, anatomically distinct from those involving the premotor areas. If true, this feature of basal ganglia organization indicates that most integration occurs at the cortical level, although some aspects of striatonigral and nigrostriatal projections could provide some integrative capacity. They might do so because of an organizational property called upward spiralling (Haber et al. 2000). The nigrostriatal projections not only go back to the loops that provide striatonigral to a given part of the substantia nigra, but they also go to adjacent loops.

Thalamus

The PF cortex, like all other cortical areas, has reciprocal connections with the thalamus. Its main thalamic connection is with the MD nucleus. The multiform part of MD, for example, receives an input from the superior colliculus (Russchen et al. 1987; Erickson et al. 2004) and projects to the caudal PF cortex, which in turn projects to the superior colliculus (Fries 1984). These connections contribute to overt and covert attention (Chapter 5).

Likewise, the medial magnocellular MD nucleus projects to the orbital PF cortex (Ray & Price 1993) and receives an input from the amygdala (Russchen et al. 1987). So, it is not

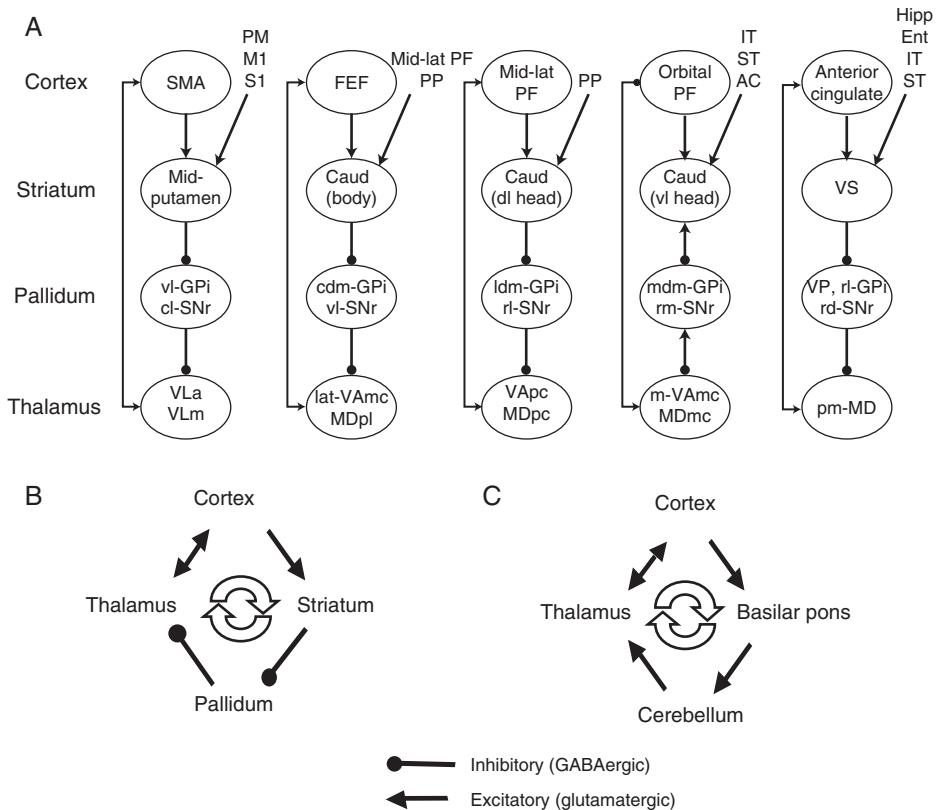


Fig. 8.1 (A) Selected cortex–basal ganglia loops. Abbreviations for cortical areas and subcortical nuclei: AC, anterior cingulate cortex; Caud, caudate nucleus; Ent, entorhinal cortex; FEF, frontal eye field; GPi, internal segment of the globus pallidus; Hipp, hippocampus; IT, inferior temporal cortex; M1, primary motor cortex; MD, mediodorsal nucleus of the thalamus; Mid-lat PF, mid-lateral PF cortex; Mid-putamen, putamen excluding the rostral and caudal putamen; PM, premotor cortex; PP, posterior parietal cortex; S1, primary somatosensory cortex; SMA, supplementary motor area; SNr, reticular nucleus of the substantia nigra; ST, superior temporal cortex; VA, ventroanterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; VP, ventral pallidum; VS, ventral striatum. Abbreviation for subdivisions: a, anterior; cdm, caudodorsomedial; cl, caudolateral; dl, dorsolateral; lat, lateral; ldm, laterodorsomedial; m, medial; mc, magnocellular; mdm, mediodorsomedial; pc, parvocellular; pl, paralamellar; pm, posteromedial; rd, rostrodorsal; rl, rostralateral; rm, rostromedial; vl, ventrolateral. (B) Overall connectional scheme for cortex–basal ganglia loops. (C) Overall connectional scheme for cortex–cerebellum loops. (A) Adapted from Alexander GE, Delong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience* 9:357–81, © 1986, Annual Reviews Inc. (B) and (C) Reproduced from Shadmehr R, Wise SP. *The Computational Neurobiology of Reaching and Pointing: A Foundation for Motor Learning*, © 2005 Massachusetts Institute of Technology, by permission of The MIT Press.

surprising that lesions of the magnocellular division of MD have effects that resemble those of lesions of the orbital PF cortex or the amygdala (Mitchell et al. 2007) (see Chapter 4). Izquierdo and Murray (2010) have demonstrated the functional interaction of the magnocellular MD nucleus and the orbital PF cortex in the reinforcer devaluation task.

Dopaminergic midbrain

Some inputs to the PF cortex come from dopaminergic neurons of the midbrain. As Chapter 3 mentions, these cells provide a reward-prediction error signal (Schultz 1998). Most theoretical work on this signal has focused on its role as a teaching signal for the striatum, but some of these cells also project directly to the PF cortex, among other areas (Gaspar et al. 1992), and they could contribute to learning at both the cortical and striatal levels (Miller & Buschman 2008).

Cerebellum

Just as with the cortex–basal ganglia loops, the cortex and cerebellum connect to each other in anatomical loops. These loops involve the basilar pontine nuclei and thalamus (Houk & Wise 1995). Among prefrontal areas, the caudal PF cortex and the dorsal PF cortex send the largest projections to the basilar pontine nuclei, with only sparse corticopontine projections arising from the ventral or orbital PF cortex (Schmahmann & Pandya 1997; Glickstein & Doron 2008). Middleton and Strick (1998, 2001) have shown that loops between cortex and cerebellum include the mid-lateral PF cortex (area 46) and the dorsomedial PF cortex (area 9).

Summary

This brief sketch of the connections of the PF cortex extracts some of the key points from Chapters 3–7, which deal with the connections of each region. We stress the convergence and integration of information in the PF cortex, as many others have before us. But Chapters 3–7 also say specifically how the primate PF cortex can do things that other parts of the brain cannot do. Some of these other structures lack sufficient intrinsic connectivity, others lack inputs about the updated valuations of specific outcomes, and others lack direct access to the premotor cortex.

The PF cortex receives a wide variety of inputs, which its intrinsic connections can integrate quickly, and it has direct influences over action. Chapters 3–7 present the evidence its cells encode conjunctions of many kinds of information. The next section puts these properties in the context of information-processing hierarchies.

Hierarchies

Fuster (2000) has long argued that we should think of the granular PF cortex in terms of hierarchies. In his view, the granular PF cortex forms the highest link from perception to action: the perception–action cycle, to use his terms. To understand the granular PF cortex, however, we need more than a concept of hierarchy and linkages between sensory inputs and motor outputs. We need to know how such linkages differ when they involve the granular PF cortex. Fuster has pointed out that they differ hierarchically. We

agree, but to convert this idea into a successful theory of the PF cortex, we need to be more precise.

To achieve this precision, we need to explain what we mean by hierarchy. In one sense, higher components lie in the hierarchy farther from either the sensory inputs or motor outputs than do lower ones. In another sense, higher levels represent information more abstractly. And in a third sense, higher levels of a hierarchy represent information with greater dimensionality, that is, with a higher degree of feature conjunction.

We recognize that the second and third senses conflict in certain ways. Abstraction, as the word implies, involves pulling out the common features of different representations, whereas higher dimensionality entails distinguishing representations by adding features. Nonetheless, we regard both abstract and high-dimensional representations as being high in the hierarchies discussed here. The abstract concept of ‘cat’, for example, includes ocelots, jaguars, and tigers, but does not have all of the features of any specific cat species and certainly not the neighbour’s tabby. In this sense, abstractions are hierarchically high even though they require fewer features. But it is also true that the synthesis of many features into a progressively more specific representation reflects the ascent along a hierarchy, as commonly construed. The pattern of feedforward and feedback connections, based on the laminar distribution of corticocortical cells and their terminals, sometimes reflects this hierarchy (Rockland & Knutson 2000).

Context hierarchy

The PF cortex lies farther from the primary sensory regions than other areas, and it receives convergent input from all of them. Jones and Powell (1970) first recognized this feature of cortical organization, basing their conclusions on studies of connectional anatomy. They pointed, for example, to the ventral visual stream, which processes information about colour, form, and visual texture. It culminates in the rostral part of the temporal lobe, including area TE and the perirhinal cortex. Because both area TE (Webster et al. 1994) and the perirhinal cortex (Petrides & Pandya 2002a) send projections to the granular PF cortex, the PF cortex can be regarded as lying at the apex of the visual processing hierarchy (Young 1992).

Similar conclusions apply to auditory (Romanski & Averbeck 2009) and tactile inputs (Jones & Powell 1970). Gustatory and visceral inputs generally parallel somatosensory pathways and follow the similar organizational principles. The olfactory system is a special case, but these inputs, too, relay from a primary olfactory area, the piriform cortex, through the agranular PF cortex to the granular PF cortex (Chapter 4). The granular PF cortex thus sits atop an information-processing hierarchy that integrates all sensory modalities to represent a current behavioural context. The PF cortex can also integrate information from the hippocampus and amygdala, along with other structures mentioned in the previous section, such as the basal ganglia and cerebellum.

The context hierarchy can be recognized from its connections, but other methods reveal the same thing. In macaque monkeys, the size of the basal dendritic tree and the number of dendritic spines increases from the V1 to V2, V4, TEO, and TE, and this trend continues into the PF cortex (Elston 2007). This hierarchy culminates in the polar PF

cortex. The increase in dendritic development probably supports an enhanced capacity for neural integration.

As Chapter 4 points out, the context hierarchy in the PF cortex extends the feature conjunctions that the ventral visual stream begins (Murray et al. 2007). At progressively higher levels of the visual hierarchy, more features enter into these conjunctions. In the granular PF cortex, inputs from agranular PF areas converge upon those from temporal and parietal cortex to establish yet higher-order multimodal conjunctions that include visual, auditory, tactile, gustatory, olfactory, and visceral features (see Figure 4.3).

Chapter 2 points out that the inferior temporal area TE, like the granular PF cortex, evolved in primates. This idea has an important implication. What evolved in primates was neither the high-level feature conjunctions of the perirhinal cortex, nor the low-level elemental representations of the striate cortex (V1) and other occipital areas. V1 and the perirhinal cortex occur in all mammals and are therefore likely to have evolved in early mammals. The inferior temporal cortex (areas TE and TEO) evolved more recently, in primates, and these areas provide intermediate levels of visual processing. Its cells represent neither whole objects nor low-level, elemental features. The inferior temporal cortex and the perirhinal cortex both send inputs to the granular PF cortex, but occipital areas do not, with the exception of the caudal PF cortex (Chapter 5). Thus most of the granular PF cortex receives inputs from the middle and higher levels of the visual hierarchy, but not from the lower levels.

Chapters 2 and 7 point to the importance of visual signs of resources. These cues also fall between objects and simple visual features. In addition, the inferior temporal cortex processes information about faces (Baylis et al. 1987; Tanaka et al. 1991), which also provide ‘signs’ or ‘cues’. Acoustic calls also act as signs, and cells in the superior temporal cortex encode specific ones such as calls (Rauschecker et al. 1995). Acoustic representations in the temporal cortex are sometimes construed as ‘objects’, by analogy with visual objects, but it is probably more useful to consider them as signs, by analogy with the middle-level visual signs. The primate brain has thus evolved to treat both auditory and visual cues as signs, and it seems to have done so by creating an intermediate level of feature conjunction in the temporal lobe, something between objects and elemental features.

Chapter 7 explains that the granular PF cortex makes use of signs as a context for goal generation, and the previous paragraph mentions face-responsive cells in the inferior temporal cortex. Given the connections between the inferior temporal cortex and both the ventral and orbital PF cortex, it is not surprising that similar responses occur in these frontal areas. Ó Scalaidhe et al. (1999) studied cell activity in the ventral PF cortex (area 12/47), as well as in the dorsal PF cortex (areas 9 and 46) and in the caudal PF cortex (area 8). They found cells that responded selectively to faces in the regions that receive inputs from the inferior temporal cortex, that is, in the ventral PF cortex, but in not the other areas. The face cells were intermixed with cells that responded to objects and coloured patterns. Importantly, none of these properties depended on prior training on a laboratory task.

Similar responses occur in the orbital PF cortex. Rolls et al. (2006) described cells there that respond selectively to faces. Some of these cells respond to face identity, others to facial expression, and others to moving heads but not to still heads. Some of these cells show selectivity for different viewing perspectives, but others respond invariantly.

All of these cells could play an important role in social interactions, and they all contribute to the context hierarchy. Facial expressions and facial identity provide important signs for social choices, much like other visual signs do for foraging choices. Acoustic signs also play a crucial role in both social and foraging choices. Like foraging choices, social choices involve the generation of a goal based on a current context in relation to current biological needs. The motivations often differ, of course.

Several findings point to the importance of integrating visual and auditory signs, and the granular PF cortex is well situated to perform this function. Cells in the lower bank of the superior temporal sulcus respond to faces and show enhanced activity when calls occur at the same time (Barraclough et al. 2005). These areas have connections with the granular PF cortex, and so it is not surprising that cells in the ventral PF cortex show similar effects (Sugihara et al. 2006).

Another example of visual and auditory integration involves conditional learning, as occurs in the paired-associate learning task (Chapter 7). Fuster et al. (2000) trained monkeys to choose a red stimulus given one tone and to choose a green stimulus given another tone. They recorded from the caudal PF cortex (area 8B) and found cells that responded selectively to one of the tones and also to the colour that was associated with that particular tone. This property corresponds to the pair coding of visual–visual associates that Chapter 7 mentions. Both the intramodal and cross-modal results reflect integration across delay intervals, a topic that we take up later.

One final example of frontal integration concerns different types of visual information, such as shape and location, the province of the ventral and dorsal visual streams, respectively. The PF cortex connects to both streams (Chapters 5–7), but Wilson et al. (1993) suggested that their signals might remain segregated in the granular PF cortex. However, Rao et al. (1997) found single cells in the mid-lateral and ventral PF cortex that encoded both remembered shapes and remembered locations. The intrinsic connections of the PF cortex thus bring together signals that first arrive in its different parts, as inputs from the dorsal and ventral streams do (Chapters 6 and 7).

These examples of context integration concern sensory information, but to specify the current context completely anthropoid primates also have to take into account goals, actions, and outcomes at a particular time and place. Connections of the PF cortex with the hippocampus probably provide some of these aspects of the context hierarchy (Chapter 3). Along with a sensory context, navigational history and information about events both play crucial roles in foraging choices.

Along with location and object identity, order and timing also play an important role in event processing. Chapter 6 explains, for example, that cells in the mid-lateral PF cortex encode order–picture conjunctions (Warden & Miller 2007). Likewise, cells in the mid-lateral and caudal PF cortex encode order–duration (Genovesio et al. 2009) and

order–distance conjunctions (Genovesio et al. 2011). Other PF cortex cells also encode stimulus order per se (Ninokura et al. 2003, 2004). Presumably these cells provide an input to cells that encode conjunctions.

In summary, the granular PF cortex integrates sensory inputs from all sensory modalities. It does so both within and across modalities, it does so for both current stimuli and stimuli that have occurred in the recent past, and it does so for both whole objects and feature conjunctions that lie between elemental features and whole objects, which we call signs. It integrates these multimodal inputs with information about events, including their order, places, and times, to function as the highest level of a context hierarchy. Other cortical areas have some of these properties, but no other cortical area has all of them, together with the direct access to the premotor areas.

Goal hierarchy

Just as the PF cortex lies relatively far from the primary sensory areas, it also lies farther from the primary motor cortex than do areas such as the primary somatosensory cortex, the premotor cortex (area 6), and rostral parts of the posterior parietal cortex (area 5). These frontal and parietal areas all send direct projections to the primary motor cortex, but the granular PF cortex does not (Jones & Powell 1970; Lu et al. 1994). Each of them also projects directly to the spinal cord, a projection that the granular PF cortex lacks (Murray & Coulter 1981).

The degree of direct access to the primary motor cortex and the spinal cord defines a hierarchy. Thus, we could describe the granular PF cortex as sitting at the top of a motor hierarchy. Alternately, because the motor system generates actions, we could call it an action hierarchy as Fuster (2008) has. Instead, we have chosen to call this aspect of PF cortex organization a goal hierarchy. We do so because we regard the granular PF cortex as generating goals, rather than actions or movements, as the previous chapters explain. We would not object, however, if readers consider the goal hierarchy as a goal–action hierarchy instead.

Along with the posterior parietal cortex, the granular PF cortex projects to the premotor cortex, and this route provides the PF cortex with its most direct influence over the control of actions. The posterior parietal cortex projects most heavily to the caudal part of the dorsal premotor cortex and to the SMA, whereas the granular PF cortex projects most heavily to the rostral part of the premotor cortex (Rizzolatti & Luppino 2001; Luppino et al. 2003) and to the preSMA (Luppino et al. 1993). Rostral parts of the premotor cortex, in turn, connect with its caudal parts. For example, the preSMA projects to the SMA, which in turn sends axons directly to the primary motor cortex (Luppino et al. 1993) and to the spinal cord (Murray & Coulter 1981). The preSMA and rostral premotor areas project to caudal parts of the premotor cortex but do not project to the spinal cord (He et al. 1995).

Thus the goal hierarchy of the frontal lobe has, at its lower level, direct access to the primary motor cortex and the spinal cord, and this hierarchy continues at higher levels into the granular PF cortex. To explain this hierarchy, we begin with the primary motor cortex.

Figure 1.10 shows that cells in the primary motor cortex (area 4) have the same kind of activity for movements guided by memory and those guided by a visible cue. Cells in the dorsal premotor cortex and the SMA often show specializations for external and ‘internal’ guidance, respectively.

Shima and Tanji (2000) recorded in the preSMA and the SMA and found cells in both areas that encoded specific sequences of action. However, cells that encoded specific transitions occurred more commonly in the SMA than in the preSMA. Conversely, cells that signalled whether the movement was the first, second, or third in the sequence occurred more commonly in the preSMA than in the SMA. Shima and Tanji used these findings to construct a hierarchical model for the production of movement sequences.

Cisek and Kalaska (2002), likewise, recorded in the rostral and caudal parts of the dorsal premotor cortex. When two potential targets appeared, some cells in the rostral part encoded both targets, but fewer cells in the caudal part had this property. When the monkey knew which target to aim for, the activity in the both parts specified that location.

The rostral premotor cortex and the preSMA, therefore, seem to lie higher in a motor hierarchy than do the caudal premotor cortex and the SMA, both on neurophysiological and neuroanatomical grounds. The latter areas, in turn, seem to lie higher in that hierarchy than does the primary motor cortex. These areas thus form a motor hierarchy.

We propose that granular PF cortex elaborates this motor hierarchy into a goal hierarchy. For example, cells in preSMA and SMA encode a given sequence of movements (Shima & Tanji 2000), but cells in the granular PF cortex encode the abstract structure of a sequence (Shima et al. 2007). As Chapter 6 explains (see Figure 6.12), of the cells with activity just before sequences, more than half encoded an abstract structure, such as alternation: pull, turn, pull, turn and push, pull, push, pull. Abstractions of this kind do not refer to specific movements, but rather to higher-order representations. There is evidence that the premotor cortex transforms these abstractions into concrete motor plans (Hoshi 2008).

In addition to abstract sequences, cells in the granular PF cortex can also encode abstract behavioural rules and strategies, such as matching and nonmatching rules (see Figure 7.9) or ‘repeat-stay’ and ‘change-shift’ strategies (see Figure 7.11). As Chapter 7 explains, these rules apply to any stimuli, and they generate sets or categories of goals to choose or to avoid. Abstract representations of a set of possible goals differ from the concrete representation of a particular goal, such as a single object or place. In this way, the representations encoded in the granular PF cortex contribute to the goal hierarchy. This concept becomes especially important when considered together with the findings about cells in the PF cortex that encode goals independent of the means of achieving them (Chapters 6 and 7).

Based on the discussion to this point, readers can appreciate that the goal and context hierarchies have many properties in common. For both, the granular PF cortex sits at the apex of an anatomical hierarchy that includes other brain areas at its lower levels. The goal hierarchy provides several ways to link a current context to the specification of a concrete action, in terms of motor commands. It does so either by specifying an object or location that serves as the target of action, by specifying the abstract structure of a series

of actions, or by specifying a rule or strategy that generates objects or locations to choose or to avoid. The ability to generate goals at a range of hierarchical levels, independent of the means of achieving them, represents an important advantage conferred by the granular PF cortex.

Outcome hierarchy

Goals lead to actions and actions lead to outcomes. Like contexts, outcomes are specified by inputs arising from various sensory modalities. However, animals did not evolve specialized reward or outcome receptors. Yet the connections of the granular PF cortex place it in a position to analyse outcomes in a unique way (Chapter 4). No other cortical area, with the possible exception of the hippocampus, has such a diverse array of inputs, and no other cortical area integrates them as effectively and at the same time has relatively direct access to the premotor cortex.

The outcome hierarchy of the granular PF cortex includes both greater feature convergence as one ascends its levels (see Figure 4.3) and greater abstraction. Chapter 4 reviews the evidence for feature convergence. Cells in the orbital PF cortex respond to visual–gustatory, visual–olfactory, and gustatory–olfactory conjunctions (Rolls et al. 1994). These combinations have obvious importance for foraging choices: they encode the specific foods or fluids that compose outcomes. In addition to encoding the physical properties of foods and fluids, cells in the PF cortex encode their biological value as updated according to current needs, as revealed by the devaluation effect (Izquierdo et al. 2004).

Chapter 4 also explains that in addition to encoding outcomes in terms of specific foods and fluids, as high-dimensional representations conjoining many features, the granular part of the orbital PF cortex also encodes outcomes in terms of an abstract, ‘common currency’, which represents value along one dimension. Both of these aspects of hierarchy play an important role in the function of the granular PF cortex. When monkeys make a choice about which goal to pursue among many options, they can compare their options in terms of an abstract valuation; when they need to learn about which choice has caused a particular outcome, they can encode the outcome in its many stimulus dimensions.

Thus both aspects of the outcome hierarchy—enhanced specificity and abstraction—contribute to the function of the granular PF cortex. Chapter 4 presents evidence that different subdivisions of the granular PF cortex subserve these two aspects of the outcome hierarchy: the lateral OFC encodes specific foods and fluids for contrasting various outcomes with each other; the medial OFC encodes value in a ‘common currency’ for comparisons.

When combined with the role of the amygdala in updating outcome valuations (Chapter 4), the primate PF cortex, as a whole, provides a powerful mechanism for integrating sophisticated representations of particular outcomes with foraging choices, including those based on abstract valuations in a ‘common currency’.

Summary

The granular PF cortex sits at the apex of three information-processing hierarchies, which include other brain structures at their lower levels. A context hierarchy builds on the

functions of sensory areas; a goal hierarchy elaborates the function of motor areas, along with the agranular parts of the medial PF cortex; and an outcome hierarchy builds on the agranular parts of the orbital PF cortex. Note that we have not yet addressed hierarchies *within* the granular PF cortex, which the next chapter takes up.

By integrating these three hierarchies, the granular PF cortex can map contexts to goals and predicted outcomes. Chapter 3 shows how the PF cortex contributes to the goal hierarchy; and Chapter 4 discusses the contribution of the PF cortex to the outcome hierarchy. Chapter 5 points to a role for the PF cortex in finding and attending to goals by integrating the goal and outcome hierarchies, for both objects and places. As for the context hierarchy, Chapter 6 discusses the generation of goals from location, order, and timing contexts; and Chapter 7 deals with the generation of goals from visual and auditory signs. All of these chapters explain the anatomical basis for these functions and list many tasks for which the granular PF cortex plays a necessary role. They also provide evidence that activity and activations generally agree.

The next three sections therefore explore the interactions among these hierarchies, interactions that generate goals based on contexts and events, and that operate when the context varies such that different goals must be generated at different times.

Generating goals based on contexts

We now turn to the generation of goals from context, which requires the integration of all three hierarchies. The conditional visuomotor task provides an instructive example of this kind of integration. A context maps to both a goal and an outcome, and monkeys must use these conjunctions to make choices. They need all three hierarchies because, over the long term, all of the contexts and goals come to have the same value. That is, the monkey cannot choose a goal based on context–outcome conjunctions or goal–outcome conjunctions; they need to use context–goal–outcome conjunctions.

Chapter 7 explains that monkeys with lesions in the granular PF cortex have severe impairments in learning the mappings between visual contexts and goals in the conditional motor task (Bussey et al. 2001). As explained in detail later in this chapter, monkeys with lesions of the orbital and ventral PF cortex do not improve beyond chance levels even after dozens of attempts at learning new conditional visuomotor associations. Normal monkeys improve on chance levels with a single experience. Neuronal activity supports a role for the granular PF cortex in conditional visuomotor learning. Asaad et al. (1998) used coloured pictures to establish the context for a saccadic eye movement. Of the task-related cells they recorded, many encoded a particular conjunction of a context and a goal.

Recall that by outcome we do not simply mean reward. Many parts of the brain have reward, reward-prediction, and reward-prediction error signals by virtue of projections from dopaminergic neurons of the midbrain, among other sources. As the previous section said, the outcome information available to the granular PF cortex, as the apex of the outcome hierarchy, includes much more specific information than dopaminergic neurons convey. Conjunctions in the granular PF cortex represent the specific sights, tastes,

smells, textures, and other features of the foods and fluids that serve as rewards in the laboratory. In the wild, these features define the foods and fluids for which animals forage.

The granular PF cortex learns many conjunctions of this kind. Table 6.1 lists some of them for the dorsal PF cortex, and the granular PF cortex as a whole encodes others, as well. These conjunctions include stimulus features and actions (Kim & Shadlen 1999), stimulus features and strategies (Genovesio et al. 2005), stimulus features and spatial goals (Genovesio et al. 2005), rules and response choices (Wallis & Miller 2003a), actions and outcomes (Barraclough et al. 2004; Tsujimoto & Sawaguchi 2004a; Hayden & Platt 2010), actions and future reward quantity (Wallis & Miller 2003b), and actions and reward value (Kennerley & Wallis 2009; Kennerley et al. 2009).

A critic might argue that other areas also encode such conjunctions. For example, the posterior parietal area LIP encodes whether a colour cue or a spatial cue specifies the direction of a saccade (Toth & Assad 2002). And neuronal activity in area MIP encodes the direction of a saccade as specified by a spatial target (Snyder et al. 1997). But, unlike the PF cortex, the posterior parietal cortex does not receive direct information about the physical properties of the outcome. Nor does it receive a substantial input from the amygdala (Amaral & Price 1984), which means that, unlike the PF cortex (Chapter 4), the posterior parietal cortex cannot evaluate specific outcomes in terms of current biological needs. Thus, as we concluded earlier based on connections alone, the posterior parietal cortex cannot do what the granular PF cortex can do, notwithstanding its importance in the primate brain (Stoet & Snyder 2009).

A critic might also point to the premotor cortex as a place with conjunctions like those in the PF cortex. Unlike the posterior parietal cortex, the premotor cortex does have connections with the amygdala, albeit weak ones that do not include all of the premotor cortex (Avendaño et al. 1983). And we have long known that lesions in the dorsal premotor cortex impair both the learning (Petrides 1987) and retention (Passingham 1985b) of conditional visuomotor tasks, which require the integration of the context, goal, and outcome hierarchies. However, the premotor cortex lacks the visual and auditory inputs that the ventral and orbital PF cortex have, and it also lacks the conjunctive representations of outcome available to many PF areas via their connections with the orbital PF cortex.

Summary

The primate PF cortex can integrate information about context, goal, and outcome, and it achieves a level of integration that other areas cannot. Many tasks require these three hierarchies and also require the PF cortex. For example, the delayed response task, which requires order-place-outcome conjunctions, depends on the dorsal PF cortex (Chapter 6). And the conditional visuomotor task, which requires sign-action-outcome conjunctions, depends on the ventral PF cortex (Chapter 7).

Chapter 2 advances the idea that these two regions, the dorsal PF cortex and the ventral PF cortex, evolved in anthropoid primates. We propose that these areas improved the ability of these animals to use sensory contexts to generate goals. Advances in vision

improved the ability to detect signs of resources at a distance, and the granular PF cortex allowed these anthropoids to order these sensory events in time and space. All of this information could then be integrated with the product of the goal and outcome hierarchies to guide the choices among foraging options. Visual advances also improved the exploitation of a current foraging site, which involves reaching and grasping. The detection of subtle visual differences among different berries, in shininess for example, can have a significant influence on foraging efficiency, as can the ability to generate an optimized sequence of goals.

To this point, we have stressed the importance of convergence and integration, which might leave the impression that the primate PF cortex functions much like the PF cortex of other mammals, but merely better in certain ways. Many theories of the PF cortex posit that it helps to generate goals based on integration, conjunctions, associations, mappings, or the same concept in other terms. So it is tempting to imagine that the primate PF cortex simply uses the profound visual advances of primates, such as foveal and trichromatic vision, to do what the PF cortex does in all mammals. But there is more to our proposal than simply a more sophisticated representation of sensory contexts. The next section suggests a qualitative advance provided to anthropoids by their new prefrontal areas.

Generating goals based on events

Event-based versus reinforcement learning

Chapter 7 explains that monkeys with experience in solving a series of conditional visuomotor problems can learn new context-to-goal mappings within a few trials. Monkeys with combined lesions of the ventral and orbital PF cortex can only do so after hundreds of trials (Bussey et al. 2001). But they can learn new mappings eventually. These findings have two implications. First, lesions of the granular PF cortex block the rapid learning of conjunctions among context, goal, and outcome. Second, other parts of the brain also contribute to learning the same information, albeit more slowly and with many more errors.

This section presents the idea that the integrative function of the granular PF cortex confers the ability to generate goals based on single events. By event we mean the context, goal, action, and outcome that occurs at a particular time and place. These unique conjunctions can reside in either short-term memory or in long-term memory.

The key to our proposal is that the use of single events underlies rapid learning and that rapid learning is one way to reduce errors. Anthropoid primates can also learn and apply abstract rules and strategies in order to reduce errors, and, as we later explain, this too requires the use of single events. Chapter 7 explains, for example, that in the conditional visuomotor task, monkeys can reduce their error rate by using a prior event to eliminate one possible choice through the ‘change-shift’ strategy.

Thus we distinguish between learning via an ancestral reinforcement-learning system and learning via a newer mechanism that depends on the granular PF cortex. The ancestral reinforcement-learning mechanism uses feedback events, usually in the form of

rewards, to strengthen or weaken associations among stimuli, responses, and outcomes. It does so relatively slowly and cumulatively, based on a weighted average of feedback events, and it evolved early in the history of animals.

Many advances occurred in early mammals, bolstered by the evolution of the neocortex. But these developments did not amount to a new learning system. As the next sections explain, we propose that primates augmented the ancestral reinforcement-learning system. As a result, they can choose goals based on single events and they can solve a broad range of problems in one or a few trials. Because the newer mechanism depends on the granular PF cortex, and because these areas evolved in primates, nonprimate mammals must rely exclusively on the older system, as the ancestors of primates did and as primates with PF cortex lesions must. It is our contention that as a result of their new learning mechanism, primates avoid many of the errors inherent in the older learning system.

Discrimination learning

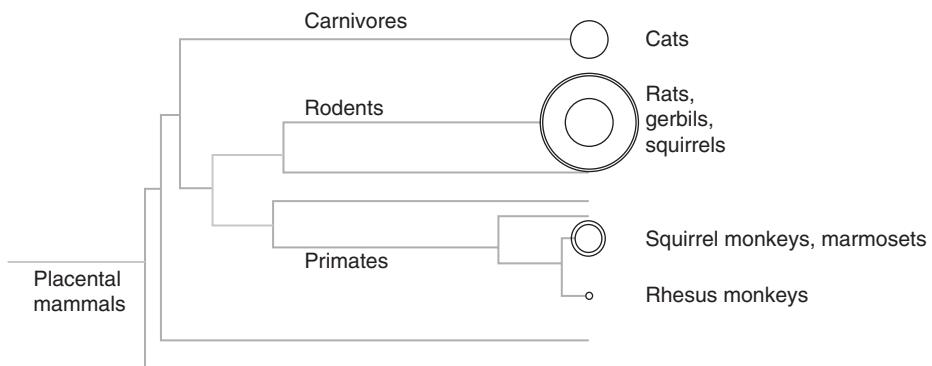
We first illustrate our point by considering discrimination learning. In this task, subjects face a choice between stimuli on each trial. Versions abound, but a typical example involves a choice between two objects. If they choose correctly, the subjects obtain a reward. All mammals, along with other animals, can solve problems of this sort. But as various species solve a series of discrimination problems, differences among them emerge (Figure 8.2).

On the first trial for each new problem, no subject can score better than chance level, and so the choices on those trials do not figure into the analysis presented in Figure 8.2. After one experience with the choice stimuli, however, animals can make a better choice the next time, on trial two. Rhesus monkeys do this very efficiently, and when they do they are said to have developed a strong discrimination learning set, often shortened to learning set. Figure 8.2B shows that the performance of rhesus monkeys improves rapidly across problems, and they come to perform at near 90% on trial two after they have solved a few hundred problems (Harlow & Warren 1952).

Yet even if they are trained on roughly the same number of visual discrimination learning problems with the same number of trials on each problem, rats and cats develop a relatively weak learning set compared to rhesus monkeys. Figure 8.2A shows a cladogram with the number of trials to 60% correct performance plotted as a circle to the right. This approach avoids the suggestion that one can rank species. Rhesus monkeys, taken to be representative catarrhine monkeys, reach 60% correct choices on trial two very quickly, as indicated by the small size of the circle. Other mammals do much less well on trial two, as indicated by proportionately larger circles. This conclusion has been challenged over the years, and Chapter 10 takes up these challenges. We argue there that results said to contradict the figure involve either flawed experimental designs or fail to focus on trial-two performance. We know of no report in the literature of macaque-level trial-two performance when a nonmammal chooses between two visual objects, as macaque monkeys do in tests of learning set.

The development of a discrimination learning set is not a simple matter. Among the factors involved, one involves learning about the structure of the task: one stimulus has a

A



B

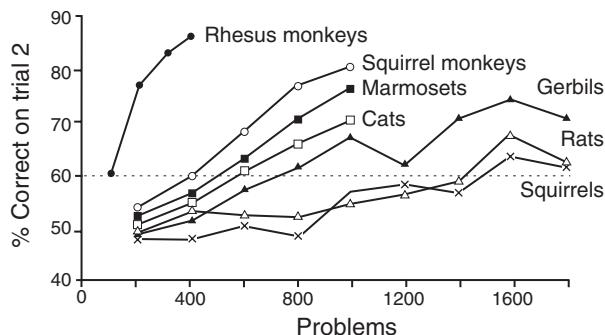


Fig. 8.2 Development of a learning set for visual discrimination problems, in a selection of mammalian species. (A) Cladogram for selected mammals on a linear timescale. The diameter of the circles at the right shows the number of problems needed to reach 60% correct on trial two, interpolated from the data presented in (B). (B) Percentage of correct choices on trial two of a novel visual discrimination problem, as a function of the number of such problems previously solved. The figure draws on studies that presented each problem for only six trials. The dashed horizontal line shows the reference for the diameter plots shown in (A). (B) Modified from Passingham *The Human Primate* © 1982 W. H Freeman and Co., Ltd.

high value, the other has no value, and subjects must choose between them. Animals approach new problems more efficiently as they learn this structure. The phrase ‘learning to learn’ refers to this factor.

Another factor involves the use of an abstract rule or a strategy. In the case of discrimination tasks, one useful strategy has been called ‘win-stay, lose-shift’. By using this strategy, a subject’s second choice depends on their first choice and its outcome: if rewarded (a ‘win’), the monkeys ‘stay’ with that choice; if unrewarded (a ‘loss’), they ‘shift’ to the alternative.

On this view, the development of a learning set has two aspects: learning that two novel objects always have a different value (the structure of the task) and learning a ‘win-stay, lose-shift’ strategy. Figure 8.2 shows that a wide diversity of mammals can do one, the other, or both. So why do macaque monkeys improve so much more rapidly than other mammals?

An observation made by Murray and Gaffan (2006) provides the key clue. Monkeys no longer achieve a near-90% correct performance on trial two if they face discrimination problems that are administered concurrently. In concurrent learning experiments, the monkeys see many pairs of stimuli, sometimes called *problems*, in each testing session. But they see these pairs only once in each session, with one trial being given for each problem. In the serial version of the task, the same problem appears trial after trial. When stimulus pairs appear concurrently, monkeys revert to the slower rate of discrimination learning that occurs in the absence of a learning set. Yet, the structure of the task and the same strategy applies.

So to develop a strong learning set, monkeys must see the same problem repeatedly, on consecutive trials, without the intervention of trials involving other problems. Murray and Gaffan (2006) suggested that in this serial version of the task monkeys learn to choose their next goal on the basis of the event that occurred on the previous trial, and that they then hold this goal in short-term memory during the intertrial interval. In other words, they prospectively code their next goal (see Chapters 6 and 7).

In the traditional learning set task, prospective coding means remembering the object that should be chosen (or avoided) on trial two. The monkey needs to notice what happened on trial one, including the context, the goal that was chosen, and the outcome that occurred, and on that basis choose the next goal, presumably on the basis of the ‘win-stay, lose-shift’ strategy. We call this choice event-based because it depends on a single event: what happened on trial one.

As monkeys gain experience with several discrimination problems in the serial format, they learn the strategy and task structure. In a sense, part of their strategy involves application of ‘win-stay, lose-shift’ and part of it involves holding the chosen goal in prospective memory. This strategy generates a goal to be attained or avoided, and this goal needs to be maintained in memory until the monkey can make its next choice. Then, when they face a new problem, macaque monkeys can perform at nearly 90% correct on trial two based on the events of trial one. The rapid increase in trial-two performance (Figure 8.2) depends in large part on how fast and how well the monkeys learn the task structure and the appropriate strategy.

It is critical to our argument that the development of learning sets depends on the granular PF cortex. Browning et al. (2007) taught monkeys a series of discrimination problems until they were able to solve them rapidly. Figure 8.3 shows the performance of their monkeys on the learning set task (grey line, unfilled circles). The investigators did not train the monkeys to the high level of learning set that others have, and so performance on trial two remained at ~70% correct, rather than the nearly errorless performance that monkeys can ultimately achieve.

Browning et al. then removed the inferior temporal cortex in one hemisphere and the frontal cortex on the other, which functionally disconnected the granular PF cortex from the relevant visual input. As a result, the monkeys lost the advantage conferred by their learning set (Figure 8.3, black line, filled circles). They reverted to the slow rate at which they had first learned to solve visual discrimination problems (not illustrated) and the

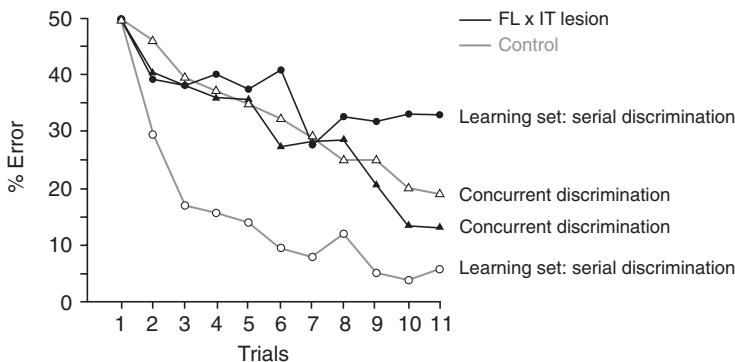


Fig. 8.3 Effect of disconnecting the inferior temporal (IT) cortex from the frontal lobes (FL) on learning set performance. Percent error as a function of trial number for serially and concurrently presented discrimination problems. In the former (circles), the same choice confronts the monkey on consecutive trials. In the latter (triangles), many choices intervene before any given choice repeats. Grey lines show the performance of normal (control) monkeys. Black lines show performance of monkeys with the crossed-disconnection lesions. Only the lesion effect for serial discriminations (learning set) was statistically significant. Reproduced from Browning PGF, Easton A, Gaffan D. Frontal-temporal disconnection abolishes object discrimination learning set in macaque monkeys. *Cerebral Cortex* 17:859–64, © 2007, with permission from Oxford University Press.

same slow rate at which they solve problems when the stimulus pairs appear concurrently (Figure 8.3, triangles).

The findings of Browning et al. show that, without normal visual inputs to the granular PF cortex, monkeys cannot achieve the kind of robust learning set that normal monkeys can. Likewise, Harlow et al. (1970) trained monkeys with bilateral frontal lobe lesions on 600 discrimination problems. Although these monkeys did show improvement over problems, they only achieved a level of 77% correct on trial two, compared to the near-90% correct performance of normal monkeys. Either Harlow's monkeys could not generate the correct choice on the basis of a single trial or they could not hold the goal in memory. Whatever the explanation, without the benefit of the interaction of the PF cortex with the inferior temporal cortex, monkeys revert to the slow rate of learning available to mammals that lack a granular PF cortex (Figure 8.2).

Reversal learning

Just as monkeys improve over a series of visual discrimination problems, they also improve over a series of visual discrimination reversals. In discrimination reversal learning, the rewarded choice changes abruptly from one choice stimulus to the other member of a pair, as Chapter 4 explains. After many such reversals, monkeys can change their choice successfully after making as few as two or three errors (Wilson & Gaffan 2008). The monkeys have thus acquired a *reversal set*, analogous to a learning set (Figure 4.7).

As in discrimination learning set, monkeys fail to show a reversal set if they must solve the problems concurrently (Wilson & Gaffan 2008). Take, for example, the choice

between two stimuli: A and B. And let us assume that the reward contingency has just changed from stimulus A to stimulus B. Under concurrent testing conditions, the monkey cannot hold the representation of stimulus B, the appropriate goal, in short-term memory during the intertrial interval because the next trial will involve a different pair of stimuli. Stimuli A and B will not reappear for several trials. As a result, just as with concurrent discrimination learning sets, monkeys revert to the slower learning rate that does not depend on event-based goal selection.

As proved to be the case for discrimination learning set, a reversal learning set depends on the interaction between the PF cortex and inferior temporal cortex. Wilson and Gaffan (2008) trained monkeys on many reversal problems and then disconnected the PF cortex from the inferior temporal cortex by the surgical procedure described earlier. The monkeys still improved as they gained more experience with reversals, but they did so at a slow rate and never achieved the level of rapid learning that they achieved before surgery.

Likewise, Izquierdo et al. (2005) showed that monkeys with lesions of the orbital PF cortex had impairments in learning a reversal set (Figure 4.7). As in the study by Wilson and Gaffan (2008), the monkeys reverted to the slower reversal learning that was typical of their first experiences with the task.

Taken together, we think that the evidence from discrimination and reversal learning shows that the granular PF cortex augments the ancestral reinforcement-learning system in a way that reduces errors. We suggest that it does so by using single events to generate goals, which in these experiments consists of an object to choose or avoid.

Delayed response and delayed alternation

Because experimenters use baited food-wells as a cue (see Figure 6.3), the classic version of the delayed response task requires monkeys to learn a ‘win-stay’ strategy, and the delayed alternation task requires a ‘win-shift’ strategy. These tasks typically have only two possible goal choices, such as left and right, which causes interference in memory as the trials unfold in a series. To perform either task successfully, the subject must base its current choice on the most recent of a series of events that interfere with each other in memory.

Chapter 6 suggests that monkeys could combat this interference, in part, through prospective coding. On the classical version of the delayed response task, this means that as soon as subjects see the baiting of either the left or right food-well, they can maintain a representation of that place as a goal during the within-trial delay period. They therefore use a single event to generate a goal, much like they do in the learning set experiments. On the delayed alternation task, it means that as soon as monkeys complete the previous trial, they can establish and maintain a representation of their goal during the between-trial delay period. Again, they can also do this by using a single event to generate a current goal.

As Chapter 6 explains, the most striking fact about the impairment caused by mid-lateral PF cortex lesions is its severity and persistence. The animals fail to improve over chance performance in 1000 trials, at which point testing usually stops (Butters & Pandya

1969). It is not clear whether they fail because they cannot relearn the rule after the lesion or because they cannot combat interference by using a prospective coding mechanism. But in either case, they fail to use single events to generate the appropriate goal, and so reduce errors. Monkeys with dorsal PF lesions can learn a spatial reversal task at either the normal rate (Passingham 1975) or at a slightly slower rate than normal (Goldman et al. 1971). On this task, the subject learns to choose the correct spatial goal over an alternative over a long series of consecutive trials. As a result, the cumulative reinforcement-learning system can guide behaviour by slowly strengthening the association of a place with a beneficial outcome, without any need to use single events.

Object-in-place scenes task

Chapter 3 introduces the object-in-place scenes task (Gaffan 1992). As explained there, monkeys see a series of background scenes, each of which contains two coloured shapes that appear in fixed locations in the foreground. As in discrimination tasks generally, to receive a reward the monkey must choose the correct coloured shape.

Chapter 3 explains that, unlike normal monkeys, monkeys with lesions of the polar PF cortex performed at chance level on trial two for a given scene and choice (Piekema et al. 2009). After this trial, the monkey resumed learning at a fairly normal rate (see Figure 3.10). The same monkeys developed a discrimination learning set normally.

Chapter 7 also presents some results from the object-in-place scenes task. Monkeys with either ventral (Baxter et al. 2007) or orbital PF lesions (Wilson et al. 2007) show mild impairments on this task. By contrast, as illustrated in Figure 8.4, bilateral PF cortex lesions cause a very severe deficit (Browning et al. 2005). A crossed disconnection of the frontal lobe from the inferior temporal cortex also causes a large impairment, but not as large as that after bilateral PF cortex lesions. After either bilateral PF lesions or these crossed lesions, the learning rate slows to approximately the level that normal monkeys can achieve without background scenes (Figure 8.4). Figure 8.4B also compares results from these frontal lesions with the magnitude of the lesion effect on trial two after polar PF cortex lesions (Chapter 3) and after transections of the fornix (Gaffan 1992).

These results show that the granular PF cortex uses the context provided by the background scenes, which leads to faster learning with fewer errors than monkeys can manage without either the background scene or without their granular PF cortex. The polar PF cortex seems to be especially important for one-trial learning.

The object-in-place scenes task resembles the concurrent discrimination task described earlier in that many trials intervene between reappearance of a given scene and its choice stimuli. We can conclude, therefore, that the benefit conferred by the scene context and the granular PF cortex does not depend on short-term memory or prospective coding. Instead, the monkeys must depend on the long-term memory of past events because the concurrent design prevents them from holding all 20 context–choice–outcome conjunctions in short-term memory until the same choice comes around again. Thus, like discrimination learning set, the key advantage comes from using single events to generate the next goal. In the object-in-place scenes task, the background scene facilitates this cognitive operation. The difference is that for the object-in-place scenes task these events

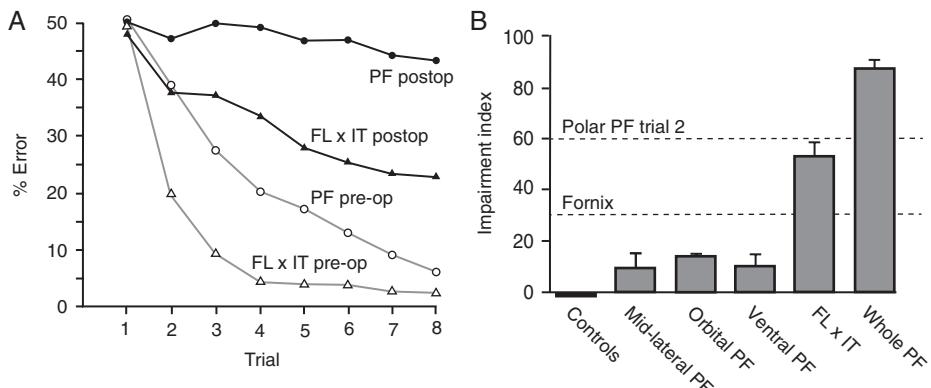


Fig. 8.4 Effect of various lesions on performance of the object-in-place scenes task. (A) Effect of bilateral PF cortex lesions (circles) and crossed disconnections of the inferior temporal cortex from the frontal lobes ($FL \times IT$) (triangles). Each curve compares preoperative (preop, unfilled symbols) and postoperative (postop, filled symbols) performance. (B) An impairment index for several lesion groups. This index plots the impairment caused by a lesion as a proportion of the maximum possible performance deficit. This normalization method removes the influence of variable preoperative performance. The dashed lines show the effects of selective lesions chosen for comparison. Error bars: SEM. (A) Reproduced from Browning PG, Easton A, Buckley MJ, Gaffan D. The role of prefrontal cortex in object-in-place learning in monkeys. *European Journal of Neuroscience* 22:3281–91, © 2005, John Wiley and Sons. (B) Adapted from Wilson CR, Gaffan D, Browning PG, Baxter MG. Functional localization within the prefrontal cortex: missing the forest for the trees? *Trends in Neurosciences* 33:533–40, © 2010, with permission from Elsevier.

are stored in long-term memory, whereas in discrimination learning set they are stored in short-term memory.

Conditional visuomotor learning

We deal with the conditional visuomotor task both earlier in this chapter and in Chapter 7. Murray and Wise (1996) showed that monkeys can learn conditional visuomotor mappings in just a few trials, and others have confirmed and generalized this result to several kinds of stimuli and movements (Brasted et al. 2005; Cromer et al. 2010). Significant learning occurs after one trial (Figure 8.5), and monkeys commonly perform without error thereafter.

Figure 8.5 demonstrates significant one-trial learning in two groups of normal monkeys. Both groups solved three-choice conditional visuomotor problems, one group by moving a joystick and the other by tapping on or maintaining contact with a touchscreen for various time intervals (tap-hold). The key trial is the third one.

On trial one, the monkeys have no stimulus-specific experience to draw upon and therefore perform at chance level. The possible use of a ‘repeat-stay’ strategy complicates trial two. On trial three, we can eliminate that complication and compare performance for two types of stimuli: one never seen before and one experienced during the first trial.

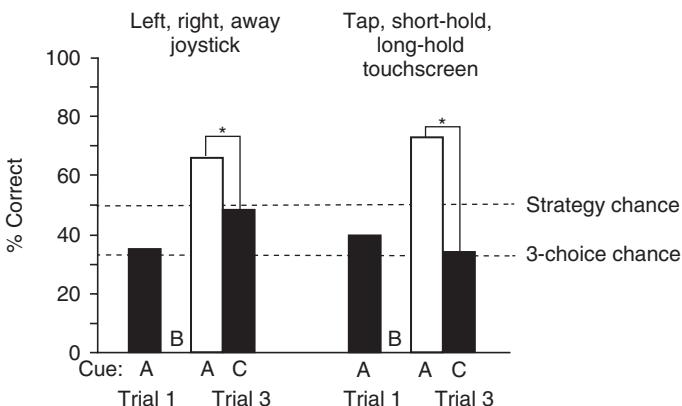


Fig. 8.5 Significant one-trial learning in the conditional visuomotor task. Two sets of data are shown: one for a three-choice task in which the monkey had to move a joystick in different directions; the other for a three-choice task in which the monkey had to either tap on a touchscreen or hold its hand on the screen for a specified period of time. Each set of three bars presents data for novel stimuli in the set [A, B, C]. On trial one, the monkeys performed at chance levels, as expected. A correction procedure then forced them to choose the correct response before that ‘trial’ ended. On trial two, a different stimulus intervened, stimulus B in this example, and performance was sometimes contaminated by strategy effects. Trial three provided the test of one-trial learning, independent of strategy effects. Black bars show the first presentation of a stimulus, white bars show the second presentation. The monkeys showed significantly better performance (asterisk) when stimulus A appeared for the second time, as opposed to when stimulus C appeared for the first time. For monkeys that spontaneously adopted the change-shift strategy (left) chance was 50% correct; for monkeys that did not (right), chance was 33% correct. Left part adapted from Murray, EA, Brasted PJ, Wise SP. Arbitrary sensory-motor mapping and the life of primates. In: L. Squire and D. Schacter, eds., *The Neurobiology of Learning and Memory*, 3rd edition, Guilford, New York, chapter 27, pp. 339-348. Right part reproduced from Brasted PJ, Bussey TJ, Murray EA, Wise SP. Conditional motor learning in the nonspatial domain: Effects of errorless learning and the contribution of the fornix to one-trial learning. *Behavioral Neuroscience* 119:662–76, © 2005, American Psychological Association.

A correction procedure ensures that the monkeys will have chosen correctly once and only once by the end of the first trial.

Monkeys tested with the joystick developed the ‘change-shift’ strategy but those performing the tap-hold version of the task did not. We do not know the reason for this difference, but it affects the scores illustrated in Figure 8.5. When monkeys happen to see a new cue on trial three, the monkeys using the ‘change-shift’ strategy perform at ~50% correct (left) and the monkeys without the strategy perform at ~33% correct (right). Putting this small difference aside for the time being, the key point is that both groups of monkeys performed significantly better when the cue from trial one reappeared on trial three (white bars in Figure 8.5). That is, they learned significantly from one prior event—the conjunction of context, goal choice, and outcome—with a different trial type intervening.

Like discrimination learning set and reversal set, it requires experience with a series of problems to develop a learning set for conditional visuomotor problems. In addition to faster learning, the application of abstract strategies also reduces errors. Chapter 7 explains the strategies. It also explained that cells in the granular PF cortex encode both fast learning and the strategies (Genovesio et al. 2005). Some cells encode the ‘repeat-stay’ strategy and others encode the ‘change-shift’ strategy. Furthermore, PF cells showed less strategy-encoding activity, if any, on error trials (Genovesio et al. 2008), which supports the idea that the granular PF cortex generates goals based on these strategies.

Unlike the discrimination and reversal tasks, the conditional visuomotor task allows a distinction between the error reduction due to learning and the error reduction due to applying strategies, also known as transfer. This contrast is possible because the three-choice version of the task has two kinds of trials: repeat trials and change trials. On change trials, the ‘change-shift’ strategy reduces a three-choice problem to a two-choice problem but does not solve the problem entirely (Figure 8.5, left). In this way, abstract learning allows transfer from previous problems to the current one. The monkeys can thus use the strategy to perform at 50% correct but must still learn the visuomotor mappings in order to reduce errors further. Without such a strategy, they perform at only 33% correct, as mentioned earlier. Like the object-in-place scenes task, the conditional visuomotor task requires long-term memory for the mappings, as well as for the strategies that implement transfer.

Like discrimination and reversal set, both rapid and abstract learning require generating a goal based on the events that occurred during the previous trial. Four points deserve emphasis:

1. Fast learning depends on events. Brasted et al. (2005) found that if their monkeys made the correct choice the first that time a cue appeared, they performed at over 80% correct if the same cue occurred on the next trial. The monkeys performed less well if an intervening trial had a different cue. This finding shows that the monkeys generated a goal and maintained it during the intertrial interval on the basis of the events from the previous trial. The monkeys also performed less well if they had made a prior error, which we explain by suggesting that the memory of the erroneous choice caused interference in memory.
2. Fast learning depends on the granular PF cortex. Bussey et al. (2001) studied change trials in order to eliminate the effects of the ‘repeat-stay’ strategy. They found that granular PF cortex lesions not only prevented one-trial learning, they blocked learning entirely over the course of ~50 trials or more (Figure 8.6).
3. The strategies depend on single events. The application of the ‘repeat-stay’ and ‘change-shift’ strategies requires monkeys to remember two events from the previous trial: the previous goal and the previous cue.
4. The strategies depend on the granular PF cortex. Monkeys with lesions of the granular PF cortex failed to apply either the ‘repeat-stay’, ‘change-shift’, or ‘lose-shift’ strategies, even though they had learned and used those strategies nearly perfectly prior to the lesion (Figures 8.6 and 8.7).

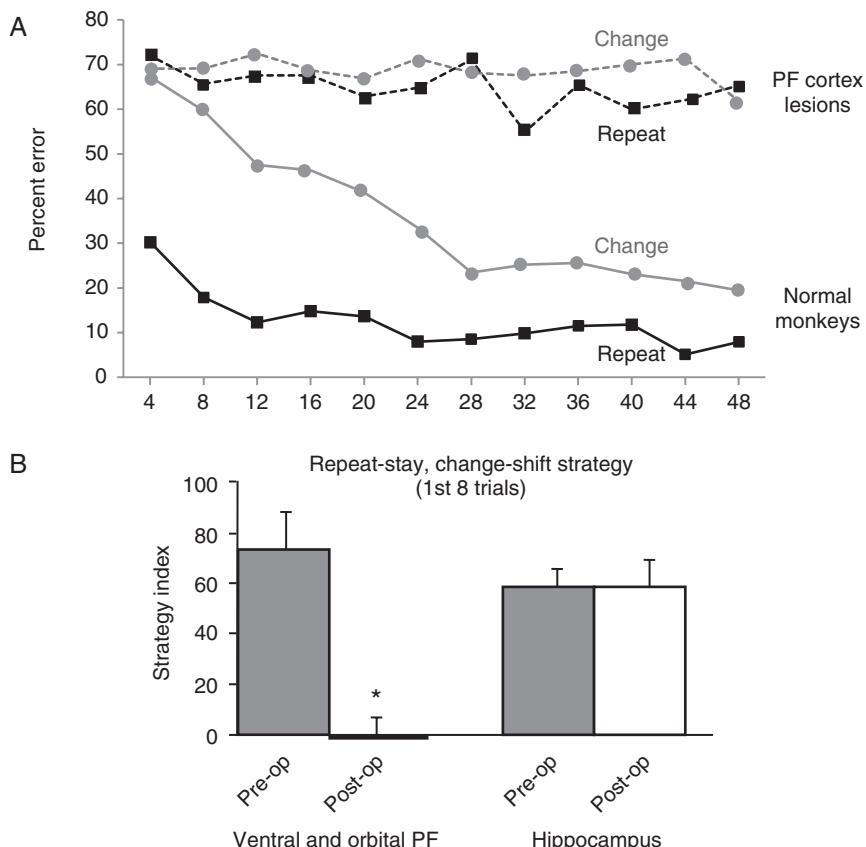


Fig. 8.6 Effect of granular PF cortex lesions on conditional visuomotor learning and the application of the 'repeat-stay' and 'change-shift' strategies. (A) Performance curves. Solid lines: preoperative performance; dashed lines: postoperative performance. Both preoperative and postoperative data are divided into repeat trials and change trials, the latter of which occurred twice as often. Postoperative performance does not differ statistically from chance level. (B) Strategy implementation. A strategy index gives the percentage error reduction achieved by implementing the 'repeat-stay' and 'change-shift' strategy as a proportion of the maximal possible reduction. This normalization method compensates for different chance levels. Left: before the lesion (pre-op) a group of monkeys that later had ventral and orbital PF cortex lesions implemented the strategies, but after the lesion (post-op) these monkeys no longer did so. The difference was highly significant (asterisk). Right: for comparison, comparable data from hippocampal lesions show no effect on strategy implementation. Modified from Bussey TJ, Wise SP, Murray EA. The role of ventral and orbital prefrontal cortex in conditional visuomotor learning and strategy use in rhesus monkeys (*Macaca mulatta*). *Behavioral Neuroscience* 115:971–82, © 2001, American Psychological Association.

A comparison with lesions of the hippocampus or one of its pathways, the fornix, provides some insight into their cooperative function. Recall that the hippocampus has extensive connections with the PF cortex (Chapter 3). Figures 8.7B shows that fornix or hippocampal lesions cause a loss of one-trial learning and two to three times more errors before monkeys solve conditional visuomotor problems: so the impairment is mild. And

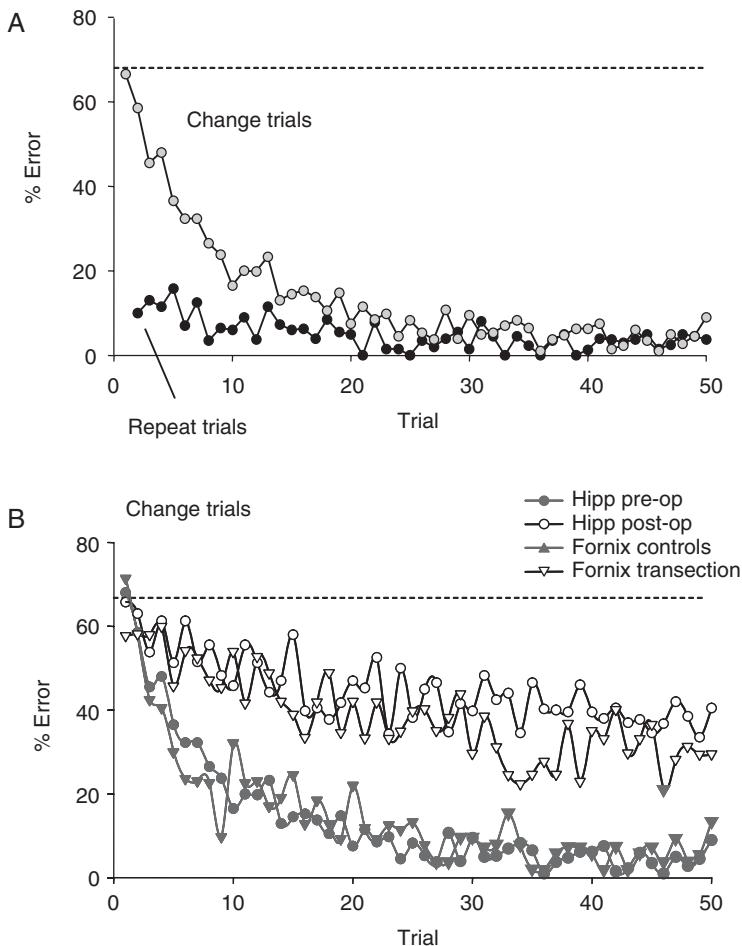


Fig. 8.7 Conditional visuomotor learning in monkeys. (A) Rapid conditional visuomotor learning on a three-choice problem in normal monkeys, as shown on change trials. Monkeys learned to move a joystick in one of three directions depending on which of three novel colour-shape cues appeared on each trial. On repeat trials (black circles), little, if any, learning is required. On change trials (grey circles), the monkeys learn the three mappings with a time constant of 7.8 trials, which is between two and three trials for each context–goal association. (B) Conditional visuomotor learning on a three-choice task: effect of hippocampal (hipp) ablations and fornix transections. For the hippocampus, the learning curves compare preoperative (pre-op, grey circles) versus postoperative (post-op, white circles) performance. For the fornix transection, the curves compare a lesion group (white triangles) to normal (control) monkeys (grey triangles). (A) Data from Murray EA, Wise SP. Role of the hippocampus plus subjacent cortex but not amygdala in visuomotor conditional learning in rhesus monkeys. *Behavioral Neuroscience* 110:1261–70 © 2005, American Psychological Association (B) Reproduced from Brasted PJ, Bussey TJ, Murray EA, Wise SP. Conditional motor learning in the nonspatial domain: Effects of errorless learning and the contribution of the fornix to one-trial learning. *Behavioral Neuroscience* 119:662–76, © 2005, American Psychological Association.

the same lesions have no effect on the strategies (Figure 8.6B) (Wise & Murray 1999; Brasted et al. 2003).

Taken together, these results show that without the hippocampus the granular PF cortex remains capable of contributing to conditional visuomotor learning in ~50–100 trials and reducing errors through various strategies (Figures 8.6B & 8.7B). Without the PF cortex, by contrast, the hippocampus can neither reduce errors within ~50 trials nor apply the relevant strategies (Figure 8.6A, B). Thus, the capacity that remains after lesions of the granular PF cortex resembles the slow stimulus–response learning of mammals that lack granular PF cortex (Chapter 2). It takes many days of training for either lesioned monkeys or other species to learn arbitrary mappings between stimuli and—depending on one’s preference in terms—responses, actions, targets, movements, or goals.

Nevertheless, a lesion to either the hippocampal system or the granular PF cortex structure causes an impairment. Thus they must work together in some way to enable monkeys to use single events to apply abstract strategies and to learn arbitrary stimulus–goal mappings in one or a few trials. As a result, monkeys make fewer errors. In fact, with some good fortune they can sometimes avoid errors altogether.

Credit assignment

Another example of using event memory to choose the current goal involves the concept of credit assignment, as Chapter 4 explains. Walton et al. (2010) studied the ability of monkeys to learn associations between object choices and outcomes. Normal monkeys could generate appropriate choices based on a memory of which choice seemed to cause a particular outcome. But monkeys with lesions of the granular OFC learned relatively slowly and cumulatively across trials. They relied on a time-weighted average of several past events, much as nonprimate mammals do, whereas normal monkeys could learn the mappings between choices and specific outcomes based on single events.

Temporally extended events

Browning and Gaffan (2008) studied what they called temporally extended events. They increased the separation between the choice and the time at which the outcome appeared. In one condition the delay was unfilled, but in another condition it was filled with a cue that provided a sign that the outcome was imminent (Figure 8.8A). Normal monkeys learned much more quickly under the latter condition, when the temporarily extended event was held together by the intervening cue. But monkeys with a disconnection between the PF cortex and the inferior temporal cortex failed to benefit in this way (Figure 8.8B).

This result resembles the other tasks discussed so far. A functionally intact granular PF cortex provides an advantage in terms of reduced errors, and interfering with its function eliminates that advantage.

The PF cortex can generate goals on the basis of temporally extended events because of its place in the three processing hierarchies. The representation of these events includes a conjunction of context, goal, and outcome at a particular time and place. Goal generation requires integration over time, or ‘cross-temporal contingencies’ in Fuster’s terminology

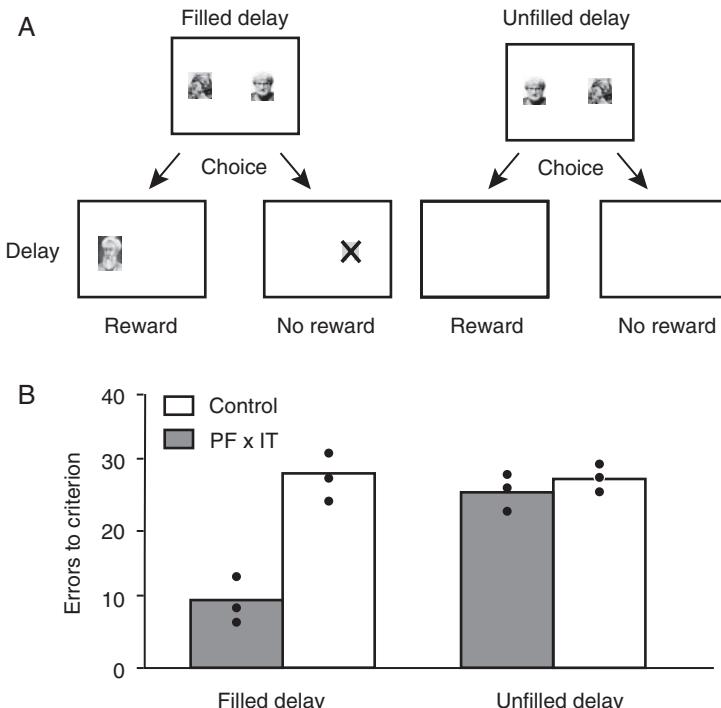


Fig. 8.8 Events on the task studying temporally extended events. (A) The top panel represents the screen seen by the monkey. After the monkey made a choice by touching one of the pictures, a delay period ensued prior to the reward, if the monkey chose correctly. In the filled-delay condition, stimulus appeared during the delay period, one specifically associated with the chosen stimulus. For the unfilled-delay condition, no picture appeared during the delay. (B) Effect of disconnecting the prefrontal cortex (PF) from the inferior temporal (IT) cortex ($PF \times IT$) (grey bars), compared to normal (control) monkeys (white bars). The bars show group means and the filled circles illustrate the performance of individual monkeys. Adapted from Wilson CR, Gaffan D, Browning PGF Baxter MG. Functional localization within the prefrontal cortex: missing the forest for the trees? *Trends in Neurosciences* 33:533–40, © 2010, with permission from Elsevier.

(Fuster 2008). Goal generation also requires integration across space because the outcome comes from a different place than either the context or the goal of action.

Additional evidence supports the view that the PF cortex integrates events over space and time in this way. Rushworth et al. (2005) taught monkeys with ventral and orbital PF cortex lesions a conditional visuomotor task and systematically varied the separation between the location of the cue and the spatial goals. Lesioned monkeys learned more slowly for greater separations, but normal monkeys did not show this effect.

Event memory versus episodic memory

We deliberately use the term event in this chapter rather than episodic memory. First, memory is not always required for choosing a goal in the accounts we propose. Sometimes,

monkeys use an event to select a future goal immediately, as in the discrimination learning set task. Second, the term episodic memory usually refers to something more specific than an event, as we use the term.

Originally, episodic memory applied to the explicit recollection of events in relation to their temporal and spatial context (Tulving 1983). We accept that no experiment has ever shown that monkeys recollect events in the sense of re-experiencing the event and their participation in it, as humans do (Suddendorf & Busby 2003). However, we do not need to make this claim. It is enough to say that an event consists of a conjunction of the context, goal, action, and outcome that occurs at a given time and place.

Recall that in our terminology the term goal refers to an object or a place and that the term outcome refers to feedback in terms of costs and benefits. Thus an event, as we use the term, takes into account the contextual basis for a choice, the object or place chosen as a goal for action, the action chosen and made, and the outcome of that action. The PF cortex seems to have access to event memories via its connections with the hippocampal system (Chapter 3) and access to current events via its connections with sensory cortex. Together, current and remembered events make up what we call a current context.

Summary

We propose that the granular PF cortex allows anthropoid primates to use a single event to improve choices. Through fast and abstract learning that depends on this capacity, anthropoids make fewer risky or wasteful choices than they otherwise would. When either lesions or experimental manipulations eliminate these advantages, the performance of anthropoid primates more closely resembles that of other mammals—and presumably that of their ancestors, as well.

Generating goals based on attentive control

In the previous two sections, we have contrasted the generation of goals based on events and current contexts with behaviours based on reinforcement learning. The reinforcement-learning system accumulates an average of many past experiences to adjust associations that guide behaviour, such as action–outcome associations. By contrast, the primate way of choosing goals involves the ability to use single events to choose objects and places as goals, and this new learning mechanism provides an advantage in a rapidly changing environment. Except in conditions of extraordinary resource volatility, the older, slower learning mechanisms work very well, which explains why nearly all of the animal kingdom can thrive without a granular PF cortex. But at a particular time and place in the history of early primates, and again during the history of anthropoids (Chapter 2), the development of new areas of granular PF cortex improved the quality of their choices and thereby provided a selective advantage.

In this section, we link the primate way of choosing goals to the concept of attention and contrast the attentive control of behaviour with automatic control. In our terminology, attention provides a goal-generation mechanism that contrasts with the automatic

choice of goals. Automatic behaviour allows animals to devote their attention to other matters, and it provides advantages in terms of the speed and reliability of behaviour.

We propose that the old reinforcement-learning system produces automatic behaviour, whereas the new system that depends on the granular PF cortex produces attentive behaviour: behaviour based on single events and the advanced kinds of current contexts that Chapters 6 and 7 describe. The distinction between automatic and attentive behaviour resembles the one between automatic and ‘controlled’ behaviour, as these terms are used in the process dissociation procedure. We emphasize, however, that we do not mean to imply anything about awareness when we use the phrase *attentive control* for monkeys.

In the laboratory, the dual task paradigm provides a test of automaticity. This procedure tests the extent to which performance of a secondary task interferes with performance of a primary task. For example, Baddeley et al. (1998) showed that when human subjects produce a random series of digits, the series becomes more stereotyped if at the same time they have to perform a memory task. Tasks differ, of course, in the degree to which they make demands on attentive processing, but the principle remains the same.

The vulnerability of a principal task to a competing task thus provides an operational definition of attentively controlled behaviour. Somehow, the principal task ‘loses’ the ‘race’ to control behaviour, or at least is disadvantaged to some degree. Accumulator networks provide a way to think about this competition. In Chapter 3, we suggest that habits can prevail over outcome-directed behaviour because the former relies on fewer and stronger associations compared to the latter. As a result, habit networks can reach threshold more rapidly and ‘win’ the competition to control behaviour. Conversely, attentively controlled behaviours probably rely on more and weaker associations than automatic behaviours. As a result, attentive-behaviour networks reach threshold more slowly than those for the alternatives and ‘lose’ the competition. By suppressing prepotent behaviours that depend on stronger associations or by enhancing attentive ones, the weaker associations can prevail.

Attentively controlled behaviour thus resembles the other forms of attention that this book discusses. Chapter 3 suggests that parts of the PF cortex generate a bias among phylogenetically older systems that compete to control behaviour. And Chapter 5 reviews evidence showing that parts of the PF cortex generate a bias among competing sensory representations elsewhere in the cortex. Likewise, we propose that parts of the PF cortex generate a bias toward goal-generation networks that rely on many, weak associations.

Imaging studies support distinction between attentive and automatic control. Toni et al. (1998), for example, taught human subjects motor sequences, and plotted the degree of PF cortex activation as the subjects improved their performance. After 45 minutes or so, the level of activation reduced to near baseline levels. Floyer-Lea and Matthews (2004) used a dual task paradigm in a similar task to show that the sequence became automatic with practise. They too found that activation in the PF cortex decreased markedly as this occurred. These findings indicate that as tasks become more automatic the PF cortex becomes less engaged.

We do not mean to imply by this statement that the PF cortex lack activity when a task has become automatic. Rainer and Miller (2002), for example, recorded in the PF cortex while monkeys performed a delayed matching-to-sample task. During the early delay period they found little activity in response to familiar objects, but the activity reappeared at the end of the delay. Thus the lack of significant activation in the imaging studies just cited probably reflects the insensitivity of the BOLD signal.

Still, the imaging results show something important about neural processing in the PF cortex. Something decreases as tasks become automatic. And, as tasks become automatic, activation increases in several areas at the same time. On motor tasks these structures include the putamen and cerebellum (Floyer-Lea & Matthews 2004), the SMA (Toni et al. 1998), and the posterior parietal cortex (Sakai et al. 1998).

It has become common in the literature to equate automatic behaviour with habits and to assume that the basal ganglia subserves habits (Fernandez-Ruiz et al. 2001; Broadbent et al. 2007). Direct evidence shows that this idea is wrong on both counts. First, there is more to automatic behaviour than habits, a point that Chapter 10 takes up. Second, only a part of the basal ganglia subserves habits.

Note that the imaging result cited previously refers to the putamen, not to the striatum or basal ganglia as a whole. Only part of the putamen showed activation. Studies in rats show that different territories in the striatum function in different aspects of automatic behaviour (Yin et al. 2008). Some parts of the striatum mediate habits, but other parts mediate outcome-directed behaviour, as Chapter 3 defines this phrase. Some have claimed that all primate behaviour, including that of humans, can be classed as either habits or outcome-directed behaviour, and they have assigned the two types of behaviour to these two striatal territories (Balleine & O'Doherty 2010). But the comparative evidence shows that primates have evolved additional territories in the striatum, such as those that receive inputs from the granular PF cortex (Chapter 2). And the next section proposes that these new parts of the basal ganglia function together with the granular PF cortex to generate goals on the basis of single events.

PF–basal ganglia loops

Neurophysiological data support this proposal. For example, Pasupathy and Miller (2005) recorded activity in the granular PF cortex and in the head of the caudate nucleus as monkeys solved novel conditional visuomotor problems. Recall that the head of the caudate nucleus is the prime striatal territory for the granular PF cortex, as opposed to the more ventral parts of the striatum, which receive their major inputs from the agranular PF cortex. In the study by Pasupathy et al., cells in both the granular PF cortex and in the head of the caudate encoded the goal progressively earlier in the trial as learning progressed. The change in activity occurred more quickly in the striatum than in the cortex, although the behavioural improvement across trials more closely resembled the slower changes observed in the PF cortex. These findings indicate that the granular PF cortex and its striatal territory become engaged during the attentive learning of visuomotor associations.

During conditional visuomotor learning, cells in the striatal territory to which the premotor cortex (area 6) projects have learning-related changes in activity that parallel those in the premotor cortex (Brasted & Wise 2004). However, in these more caudal areas, changes in learning-related activity follow the improvement in performance, rather than preceding it, as occurs in the striatal territory of the granular PF cortex. Furthermore, the activity changes continue as subjects practise the movement and it progresses toward automaticity.

This evidence suggests that the granular PF cortex and its striatal territory mediate attentive behaviour, whereas more caudal cortex–basal ganglia loops mediate automatic behaviour. More recent evidence supports this conclusion. Antzoulatos and Miller (2011) recorded neuronal activity in the granular PF cortex and its striatal territory. Their monkeys learned to map visual categories to either a left or right goal for a saccadic eye movement. Antzoulatos and Miller first confirmed the finding just mentioned for conditional visuomotor learning. When the monkeys could learn to map exemplar stimuli to a goal, striatal activity encoded the goal earlier than did cortical activity. However, as the monkeys learned to classify many exemplars in each category, cortical activity that encoded the category-to-goal mappings developed earlier than did striatal activity. Thus, taken together, the granular PF cortex and its striatal territory function to support of attentive, as opposed to automatic, behaviour.

Miyachi et al. (1997) provided further evidence for the distinction between a rostral striatal system for attentive behaviour and a more caudal one for automatic behaviour. They taught monkeys sequences of movements and overtrained them until the sequences had become automatic. They then inactivated either the rostral striatum or more caudal parts. The rostral inactivations included the head of the caudate nucleus and the most rostral part of the putamen, which receive inputs from the granular PF cortex. The more caudal inactivations included parts of the putamen that receive inputs from primary motor cortex and premotor cortex.

Miyachi et al. showed that inactivating the rostral striatum impaired new learning, whereas inactivating more caudal parts impaired automatic performance. Furthermore, as performance becomes automatic, activity in the rostral striatum decreased and activity in the middle striatum increased (Miyachi et al. 2002), in accord with the findings of Brasted and Wise (2004).

Thus, as a task becomes automatic a shift occurs from *attentive control* by the granular PF cortex and *its* striatal territories to *automatic control* by the premotor cortex and *its* striatal territories.

To test whether the connections between the premotor cortex and striatum are essential once a motor task has become automatic, Nixon et al. (2004) taught monkeys a conditional visuomotor task and overtrained them for 3 months. The behaviour thus became automatic. The authors then disconnected the striatum from the premotor cortex by making two lesions, one in each hemisphere (Figure 8.9B). On one side, they lesioned the globus pallidus, which conveys striatal outputs to the premotor cortex via the thalamus. On the other side they lesioned the premotor cortex. This combination of

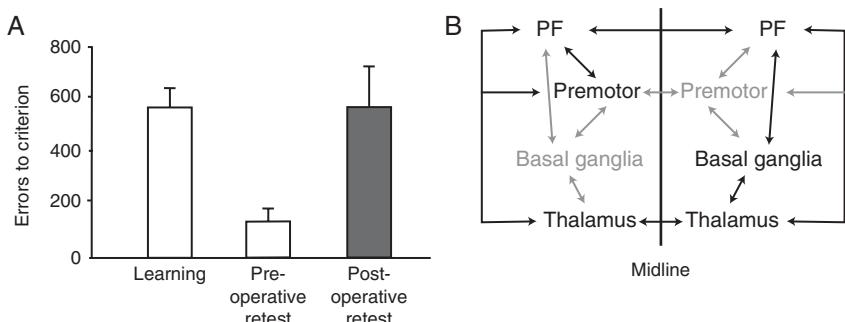


Fig. 8.9 Effect of disconnecting the premotor cortex from the basal ganglia on performance of the conditional visuomotor task. (A) The white bars give the number of errors for initial learning and, after a hiatus in testing, for a preoperative ‘relearning’ test. The grey bar shows the number of trials needed to relearn the task after the lesion (postoperative test). (B) Illustration of the lesions and the connections involved. Grey: the lesioned structures and affected connections in each hemisphere. Black: intact structures and connections in each hemisphere. Reproduced from Nixon PD, McDonald KR, Gough PM, Alexander IH, Passingham RE. Cortico-basal ganglia pathways are essential for the recall of well-established visuomotor associations. *European Journal of Neuroscience* 20:3165–78, © 2004, John Wiley and Sons.

lesions abolished all memory of the task. The animals took as long to relearn it as they had to learn it in the first place (Figure 8.9A). Relatively automatic control of behaviour thus depends on interactions between the premotor cortex and its striatal territories.

PF–cerebellar loops

Like the loops that involve the striatum and the granular PF cortex, there are loops that involve the cerebellum and the granular PF cortex, specifically the mid-lateral PF cortex (Kelly & Strick 2003). Other loops involve cerebellum and the premotor and primary motor cortex (Strick et al. 2009). We have already mentioned that activation increases in the cerebellum as a motor sequence task became automatic (Floyer-Lea & Matthews 2004). Some of these activations occur in the dentate nucleus, which projects back to the cortex via the thalamus.

To see whether cerebellar lesions caused impairments on tasks sensitive to PF cortex lesions, Nixon and Passingham (1999) made lesions in the dentate and interpositus nuclei. The monkeys could relearn the delayed alternation task, which lesions of the granular PF cortex badly impair. And, in a subsequent study, monkeys with the same lesion could learn a new sequence of movements. However, on a measure of reaction times, they never achieved the same level of automaticity as normal animals (Nixon & Passingham 2000). Lu et al. (1998) also taught monkeys a number of different movement sequences, and they overtrained the animals on a subset of them. During inactivation of the dentate nucleus, the monkeys could learn new sequences normally, but they showed impaired eye-hand coordination for the overtrained, automatic sequences. Taken together, these findings support a contribution of the cerebellum to the timing of automatic behaviour.

In support of this idea, Ramnani and Passingham (2001) reported an increase in activation of the cerebellar cortex as subjects learn the timing of movement sequences until they became automatic. These changes occurred in the cerebellar lobule that connects with the PF cortex. Nixon and Passingham (2001) found that monkeys with lesions in the dentate and interpositus nuclei fail to show the improvement in reaction time that occurs when targets occur at predictable, as opposed to unpredictable, times. So the specific contribution of the cerebellum to automatic behavioural control might involve the timing of actions rather than the choice of actions.

Engaging attentional control

In an environment with stable resources, it pays to behave quickly and automatically, relying on an average of previous events. When this behaviour fails to produce a consistent outcome, it makes sense to switch to attentive control. The switch to an attentive mode of control could be triggered by reward-prediction error signals or by the other signed and unsigned error signals that Chapter 3 mentions, and these signals could arise from any of several sources, including midbrain dopaminergic cells or cells in the amygdala.

Rowe et al. (2002a, b) used imaging in humans to study the switch from automatic to attentive control. Their subjects performed simple motor sequences with four fingers. Moving four fingers in a fixed sequence requires little attention, and no significant activation occurred in the granular PF cortex in this situation (Rowe et al. 2002b). But when the subjects were instructed to attend to their actions, significant activation occurred in the granular PF cortex, along with the preSMA. Lau et al. (2004a) reported activation in the same two areas when they manipulated the subjects' attention by requiring them to report the time at which they first became aware of their intention to move. In sum, activation occurs in the granular PF cortex and in the preSMA when people attend to their actions or intentions, thus engaging attentional control. In Chapter 9 we take up these findings again when we consider additional levels of hierarchy in the human PF cortex.

Summary

This section emphasizes that as a behaviour becomes automatic, attentive control by the granular PF cortex and its striatal territories gives way to automatic control by the premotor cortex and its striatal territories.

Some might ask where this leaves the *agranular* PF cortex and its striatal territories. In a sense, they lie between the loops involving the granular prefrontal cortex and the premotor cortex. Chapter 3 reviewed evidence that the agranular PF cortex biases brain structures that mediate habits (S–R associations) and conditioned outcome-directed behaviours (R–O and S–R–O associations). We proposed a bias toward the kind of association that is most appropriate to the current behavioural context. This idea suggests that the agranular parts of the PF cortex, like the granular parts, play a role in the attentive control of behaviour. But agranular areas differ from granular ones in that they do so by regulating automatic control: the product of the reinforcement-learning system. Such

functions could be viewed as in-between those of granular PF–basal ganglia loops and premotor–basal ganglia loops.

Fundamental function of the PF cortex

To this point in the chapter, we explain that the connections of the granular PF cortex put it in a unique position: it sits at the apex of context, goal, and outcome hierarchies. And we review evidence showing that it functions to generate goals based on a sophisticated current context and based on single events. As a result, the granular PF cortex reduces errors and speeds learning during the attentive, as opposed to automatic, control of behaviour. This capacity represents a qualitative change in the control of behaviour, from the phylogenetically older mechanisms that depend on slowly adjusted stimulus–response–outcome associations to a new mechanism based on attended, one-time events. In the broadest sense, the granular PF cortex confers on primates a new way of knowing what to do in nonroutine situations (Wise 2008), and these are the situations that require attentive control.

Given all this, the time has come to propose a fundamental function for the granular PF cortex that has more specificity and greater testability than ‘knowing what to do in non-routine situations’. What we have said so far has depended on a top–down approach to the problem. We wanted to see if our idea accounts for the available evidence. Next we use a bottom–up approach to see if we can build from observations to the same idea.

Behavioural and physiological fingerprints

Table 8.1 lists some tasks on which monkeys with PF cortex lesions perform poorly. Collectively they constitute a behavioural fingerprint, as Chapter 1 explains. The table also suggests the some components of behaviour required by the various tasks.

Table 8.2 lists some of the properties of PF cortex neurons. Collectively they constitute a physiological fingerprint. To permit reference to the tables, each task (T) and cell-activity category (C) has a letter and number designation. For example, T1 refers to the delayed response task (Table 8.1) and C1 refers to retrospective delay-period activity (Table 8.2).

We see six main themes about PF cortex function arising from these tables: integration, interference, flexibility, prospection, sequences, and valuations. No doubt, other authors would list different tasks and additional cell properties. They could emphasize different themes, such as categorization, abstraction, set, inhibition, planning, monitoring, and attention. Some of these differences represent genuine disagreements, and Chapter 10 takes up some alternative views of PF cortex function. Some merely represent differences in terminology: attention resolves interference; prospection involves set and planning; and categorization results from integration.

1. Integration. Many of the tasks in Table 8.1 depend on the integrative function of the PF cortex, which we discussed earlier in terms of conjunctions. Conditional tasks (T6–8) depend on context–goal–outcome conjunctions, the object-in-place scenes task (T19) requires the use of the background for context conjunctions, and the

Table 8.1 Tasks

Tasks	Components
1. Delayed response	Flexibility, order, interference, prospection, integration over time
2. Delayed alternation	Flexibility, order, interference, prospection, integration over time
3. Search (recurrent)	Flexibility, interference, prospection
4. Ordered object (recurrent)	Flexibility, interference, prospection
5. Temporal order	Interference, sequences, order, discriminating items in memory
6. Visual conditionals	Flexibility, prospection if delayed, integration
7. Auditory conditionals	Flexibility, prospection if delayed, integration
8. Visual matching (recurrent)	Flexibility, prospection if delayed, integration
9. 'Repeat-stay'/'change-shift'	Event memory from previous trial, interference, prospection
10. Go no-go	Flexibility, inhibiting action
11. Stop signal reaction time	Inhibiting action
12. Antisaccade/prosaccade	Flexibility, inhibiting action (antisaccade)
13. Reversals	Flexibility
14. Dimensional shifts	Flexibility, shifts of attention
15. Wisconsin card-sorting task	Flexibility, abstract rules, shifts of attention
16. Planning	Prospection, preparing a sequence
17. Generating a sequence	Flexibility, recency/order, interference, prospection in ITI
18. Strategy tasks	Flexibility, abstract sequences, sets or classes of contexts, goals
19. Scene learning	Integration
20. Discrimination learning set	Transfer, prospection in the ITI
21. Reversal learning set	Transfer, flexibility, prospection in the ITI
22. Devaluation	Updating valuations, integration

Key:

Abstract: applicable to novel stimuli, rather than concrete exemplars.

Event memory: memory of a goal, action, and outcome in the spatial and temporal context in which it occurred.

Interference: interference between items or between trials in memory.

ITI: intertrial interval.

Prospection: preparing a specific goal, often without current sensory inputs from that goal.

Recency: the most recent or last trial is relevant.

Recurrent: the same two or three choices are available on all trials.

Scene memory: memory of items in their unique scene.

Transfer: applying an abstract rule or strategy to a novel behavioural problem.

devaluation task (T22) requires conjunctions of the sight, flavour, and current value of specific foods. Many kinds of cell activity also reflect such conjunctions (C5, C6, C28), as Chapter 6 discusses (see Table 6.1).

2. Interference. Table 8.1 lists interference for several tasks, and the resolution of interference depends on attention to the relevant item among distractors. Chapter 6 explains that on both the delayed response (T1) and delayed alternation (T2) tasks,

Table 8.2 Cell activity

Activity	References
Delayed response	
1. Retrospective activity encoding the cue during the delay	Niki and Watanabe (1976)
2. Prospective activity encoding the goal during the delay	Niki and Watanabe (1976)
Temporal order	
3. Activity encoding the more recent of two items	Warden et al. (2007)
Conditional motor learning	
4. Activity encoding the cue or response	Asaad et al. (1998)
5. Activity encoding the association between cue and response	Asaad et al. (1998)
6. Activity encoding new conditional visuomotor mappings	Pasupathy and Miller (2005)
Paired-associate learning	
7. Retrospective activity encoding the cue early in the delay	Rainer et al. (1999)
8. Prospective activity encoding the goal later in the delay	Rainer et al. (1999)
Abstract strategies	
9. Retrospective activity encoding the goal on the prior trial	Genovesio et al. (2006a)
10. Prospective activity encoding the current goal	Genovesio et al. (2006a)
11. Activity encoding the 'repeat-stay' strategy	Genovesio et al. (2005)
12. Activity encoding the 'change-shift' strategy	Genovesio et al. (2005)
Cue relevance	
13. Activity encoding the currently relevant cue	Lauwereyns et al. (2001)
14. ITI activity encoding the currently relevant dimension	Mansouri et al. (2006)
Current rule	
15. Delay-period activity encoding the current rule	Wallis et al. (2001)
Generating a movement or sequence	
16. Prospective activity when generating a sequence of goals	Procyk and Goldman-Rakic (2006)
Planning sequences	
17. Prospective activity encoding one of three movements	Mushiake et al. (2006)
18. Prospective activity encoding abstract sequences	Shima et al. (2007)
Switch after errors	
19. Prospective activity when generating switches after errors	Barraclough et al. (2004)
20. Prospective activity encoding planned switches after errors	Shima and Tanji (1998)
Countermanding a saccade	
21. Activity cancelling a planned saccade	Hanes et al. (1998)
Reward expectancy	
22. Prospective activity encoding an expected reward	Watanabe (1996)
23. Prospective activity encoding a preferred reward	Tremblay and Schultz (1999)
24. Activity encoding the amount of reward	Wallis and Miller (2003)

Table 8.2 (continued) Cell activity

Value of reward	
25. Activity encoding reward value	Critchley and Rolls (1996)
26. Activity encoding the abstract value of reward	Padoa-Schioppa and Assad (2006)
Choice & reward	
27. Activity encoding conjunction of action choices & reward	Matsumoto et al. (2007)
28. Activity encoding conjunctions of object choices & reward	Wallis and Miller (2003)
29. Return of activity encoding the choice at feedback time	Tsujimoto et al. (2009)
Interaction of probability, rewards, & cost	
30. Activity encoding probabilities, rewards, and effort cost	Kennerley et al. (2009)
Prediction error	
31. Activity encoding prediction errors	Matsumoto et al. (2007)
Attention	
32. Activity encoding attended locations	Lebedev et al. (2004)

monkeys have a series of locations in memory. However, only the most recent location provides the context for choosing the current goal in order to obtain the desired outcome. The others act as distractors. Chapter 6 presents a similar account for objects on the ordered object task, more commonly called the self-ordered task (T4). Consistent with this demand, PF cortex cells encode order (C3) and conjunctions with order (see Table 6.1).

- Flexibility. Table 8.1 lists flexibility for many tasks. Conditional tasks (T6, T7) and strategy tasks (T9) require monkeys to change their goal from trial to trial. Sometimes conditions change less frequently, over blocks of trials, as on reversal tasks (T13, T20). Reversals cause a reward-prediction error signal, and cell activity in the PF cortex reflects such errors (C31). Cells reflect a shift in goals during reversal (C19), conditional (C5, C6), and strategy tasks (C9, C12).
- Prospection. Table 8.1 lists prospection for many tasks, and prospective coding, in the sense that we use the term, involves the short-term memory of the objects and places that serve as goals. As explained earlier, prospective coding contributes importantly to discrimination learning sets and reversal learning sets. In those tasks, monkeys use events to generate goals, and prospective coding maintains these goals in short-term memory over the intertrial interval. On the delayed response task (T1) prospective coding maintains the goal in memory during the delay period and protects it from interference from goals chosen on previous trials. Prospective coding occurs both during within-trial (C8, C10) and between-trial (C10) delay periods.
- Sequences. Many tasks require the ability to generate a sequence of goals (T17), and cell activity encodes each goal in a series (C16). The ability to plan a series of subordinate goals (T16, T17) involves subpopulations of cells that code for the different components of the series (C17), which play out over a wide variety of time frames.

The delayed alternation tasks (T2) can also be regarded as involving sequences in that the current goal depends on the previous one.

6. Valuation. Monkeys learn all of the tasks in Table 8.1 by processing reward feedback, so valuation is involved in all goal choices. For example, what makes a rule the current rule (T15) is the fact that, if followed, it leads to a beneficial outcome. Many cells in the granular PF cortex (C22–30) show various types of outcome-related activity, as Chapter 4 discusses.

Proposal

Our bottom-up approach produced a list of themes, and our top-down approach interpreted results from many tasks. To discern the fundamental function of the primate PF cortex, however, we need to synthesize everything. To meet this challenge, we submit a proposal, first in brief form and then in a slightly elaborated version, followed by notes on terms and concepts. This proposal represents the culmination of the proposals for each major region of the PF cortex that Chapters 3–7 set forth.

In brief:

The granular PF cortex generates goals that are appropriate to the current context and current needs, and it can do so based on a single event.

Expanded:

The fundamental function of the granular PF cortex, as a whole, is to generate the goals—objects and places that serve as targets of action—that are appropriate given the current context and desired outcome, as evaluated in terms of current biological needs. In contrast to phylogenetically older learning systems, it can do so attentively, on the basis of a single event. As a consequence, it provides a mechanism for reducing errors, and it does so in two ways: by fast learning and by providing a mechanism for learning and applying abstract rules and strategies. When necessary, the PF cortex maintains goals and sequences of goals in prospective memory until an attempt can be made to achieve them.

Because many of the terms that we use have different meanings in various fields of research, we add the following explanatory notes:

- ◆ The ‘current context’ includes the stimuli that are currently available to sensory receptors as well as recent events that are relevant to generating the current goal.
- ◆ By ‘generates … goals’ we exclude behaviour that is habitual, conditioned, automatic, prepotent, or routine.
- ◆ By ‘current needs’ we refer to the fact that, after consuming a particular resource in some quantity, the biological need, drive, or motivation for that resource decreases.
- ◆ By ‘goal’ we refer to an object or location that serves as the target for an action. We distinguish goal, in this sense, from an outcome.
- ◆ By ‘event’ we refer to the conjunction of a context, goal, action, and outcome at a particular time and place.

- ◆ By ‘generates goals ... based on single events’ we distinguish goal choices based on one event from slow learning on the basis of reinforcement as averaged over several events.
- ◆ By ‘abstract rules’ we refer to cognitive operations exemplified by the matching-to-sample rule. Abstraction refers to the fact that a particular task operation applies to any stimulus items, novel or familiar.
- ◆ By ‘strategy’ we mean either a partial solution to some behavioural problem or one among two or more solutions to a problem. Strategies are necessarily abstract, in the sense used for abstract rules
- ◆ By ‘prospective memory’ we mean the encoding and maintenance of goals in short-term memory.

Consequences

If our proposal has merit, then the fundamental function of the primate PF cortex must have many consequences. Table 8.3 summarizes some them, organized according to the information hierarchies (context, goal, and outcome) and themes (integration, resolving interference, flexibility, prospection, sequences, and valuations) discussed earlier. Take the context hierarchy and the theme of integration as an example. The table points to the fact that primates can integrate information across all sensory domains, that they can integrate events across time, and that they can integrate contexts, events, actions, and

Table 8.3 Cognitive capacities and processes that reduce errors in anthropoid primates as a result of its fundamental function.

Hierarchy	Cognitive capacity	Cognitive processes and representations
Context	Integration	Integration across delays: cross-temporal contingencies, working memories Integration across events: temporally extended events Integration across domains: multimodal feature conjunctions Integration across exemplars: categorization, abstractions
	Interference	Top-down biased competition among sensory representations Top-down bias among representations in memory
	Flexibility	Maintaining goals while varying means to achieve them
	Prospection	Maintaining goals until the opportunity to achieve them arises
	Sequences	Planning across subordinate goals to achieve an ultimate goal Planning across exemplars: categorization of sequences
Goal	Valuation	Sensitivity to changing needs: updated valuation based on current state Valuation of events: credit assignment
	Integration	Integration across domains: multimodal feature conjunctions (appearance, flavour)

outcomes. Integration across time results in ‘cross-temporal contingencies’; integration across events leads to sequences and ‘temporally extended events’; integration across sensory domains generates multimodal feature conjunctions; and integration across exemplars results in categorization and abstractions. The table continues this list for the remaining hierarchies and functional themes.

When we put it all together, the fundamental function of the primate PF cortex appears to us to have one overarching consequence: a decrease in the number foraging choices that fail to produce the most beneficial outcomes possible, waste effort, or incur an enhanced risk of predation. In laboratory testing, this function leads to fewer errors and faster learning on a wide variety of behavioural tests:

1. Given sufficient experience, monkeys can learn visual discriminations (Figure 8.2), conditional visuomotor mappings (Figure 8.5), and object-in-place conjunctions (Figures 3.10 and 8.4) in a single trial.
2. They can use their experience with similar problems to learn and apply abstract rules and strategies. Abstract rules and strategies apply to any stimulus material, so psychologists sometimes call this capability transfer (Warren 1966). Such transfer can reduce errors prior to learning about exemplars (Bussey et al. 2001).
3. They can choose future goals on the basis of a current event and hold these goals in prospective memory, as they do in learning set tasks (Murray & Gaffan 2006; Wilson & Gaffan 2008).
4. They can assign an outcome to a single choice among objects (Walton et al. 2010).
5. They can combine these error-reducing mechanisms because their granular PF cortex works as a whole.

Adaptive advantages

The laboratory tasks just mentioned might seem remote from the everyday foraging behaviours of primates. But as Chapter 2 explains, primates tend to live long lives and anthropoid primates tend to rely on volatile food resources. Accordingly, anthropoids can benefit greatly from using single or infrequent events to guide their foraging choices. And the ability to reduce foraging errors has crucial advantages. Life can be cruel, offering only a few chances for success and many dangers. In a volatile environment, full of competitors and predators, the consequences of even a single error can be severe, even fatal.

In Chapter 1 we promised to explain not only what the primate PF cortex does and how it performs that function, but also the selective factors underlying its development. In order to fulfil this aim, we recast our proposal in terms of foraging choices:

The granular PF cortex evolved in primates as an adaptation for reducing the number of unproductive, risky, or costly foraging choices that phylogenetically older learning mechanisms produce. These older mechanisms depend on the slow, cumulative strengthening of associations based on reinforcement, averaged over many feedback events. The new mechanism that primates evolved brings single events—conjunctions of contexts, goals, actions, and outcomes—to bear on the choice of foraging goals. The

information available to this new prefrontal mechanism depends to a large extent on the visual advances that evolved in primates.

Note that we do not claim that the granular PF cortex of primates confers a unique ability to learn from single events or to choose goals on that basis. To say that primates can do something does not imply that other animals cannot. Rats, along with many other animals, never eat novel foods again if nausea follows their consumption, a phenomenon called the taste-aversion effect (Rozin & Kalat 1971). And some species show imprinting: the long-term recognition of an individual from one viewing event (Bateson 1969).

We suppose that many other special-purpose learning mechanisms have evolved, as well, which could mediate one-trial learning in their specific domains. In Chapter 1, we discuss the fact that rats can use single events to reject one arm of a radial maze as a current goal (Olton et al. 1982): a prepotent ‘win-shift’ strategy. Chapter 3 explains that rats spontaneously perform the nonmatching-to-position task, which draws on their prepotent behaviour in response to a single prior event. And we know that rats can use context, such as the texture of a maze’s floor, to remember a visible object and its location based on one experience (Eacott & Easton 2010).

We accept all of this and more. What we claim, however, is that the primate way of reducing errors applies more generally and to a wider range of foraging problems than such specialized systems can manage. The advantage thus conferred may seem subtle, but it might have been vital to the success of anthropoid primates.

Earlier, we listed six themes that seem to emerge from the voluminous literature on the PF cortex: integration, interference, flexibility, prospection, sequences, and valuation. We can now suggest how each of these abilities might contribute to foraging choices.

1. **Integration.** Primates can integrate foraging information across all sensory domains to represent a current context. Chapter 2 explains how the ancestors of modern anthropoids took to diurnal life and developed a fovea that eventually supported trichromatic vision. The same chapter explains that the dorsal and ventral visual streams, which include new posterior parietal and temporal areas, also evolved in primates. Foveal vision allows anthropoids to notice, at long distances, many fine aspects of trees and, when close enough, to see which animals, leaves, and fruits might be there. The PF cortex plays the key role in integrating information from the dorsal and ventral streams with each other and with information from the other sensory modalities.

This information allows primates to make better choices regarding both what patch of resources to explore and what items to obtain (or avoid) within a patch—and in what order. Choices among distant patches eventually involve navigation, and so hippocampal function needs to be integrated with that of the PF cortex (Chapter 3). Choices about what to obtain within a patch eventually involve hand movements controlled by the premotor cortex, specifically reaching and grasping in the vision-dominated frame of reference that primates evolved. These behaviours often involve the integration of visual with somatosensory information. Manipulation, palpation,

and haptic exploration depend in large part on inputs from a ‘tactile fovea’, which represents another primate innovation (Chapter 2). Furthermore, their auditory system detects calls and other sounds that primates or birds make as they forage in a given site (Chapter 7), and integrates this information with vision.

2. **Interference.** Interference in memory presents a particular problem to foraging anthropoids. They forage mainly on fruits, insects, and leaves, which occur in patches with many similar items in view. Most of these other items cannot fulfil their current biological needs. Top-down attention can bias the processing and memory of sensory inputs toward those that are relevant to those needs. As Chapter 6 says, the dorsal PF cortex seems to play a key role in mitigating interference from irrelevant events, in part based on their order in time. Chapter 5 explains the role of the caudal PF cortex in mediating top-down attention to relevant features of the sensory environment.
3. **Flexibility.** In Chapter 2, we point to evidence that anthropoid primates evolved to exploit volatile resources such as fruits and tender leaves. In such circumstances, it pays to be flexible. An anthropoid primate can behave flexibly, in part, because if its first choice of action does not achieve its goal and produce the desired outcome, it can maintain the goal in memory and shift to a different action. A key advance provided by the anthropoid PF cortex thus involves the generation, maintenance, and long-term storage of goal representations independent of the action needed to achieve that goal. It is in large measure for this reason that the elaboration of an action hierarchy into a goal hierarchy is of such importance. This chapter explains the importance of the granular PF cortex to the goal hierarchy.
4. **Prospection.** If a goal can be represented independent of *how* it could be achieved, it can also be represented independent of *when* it could be achieved. Prospective coding can maintain a temporally distant goal in memory, and Chapters 6 and 7 discuss the role of the dorsal and ventral PF cortex, respectively, in this function.
5. **Sequences.** Goals can be combined in sequences and hierarchies. Chapter 6 explains that when a goal requires a sequence of actions or subordinate goals, anthropoid primates can prepare each of the elements in the sequence in advance, together with the specification of their order and timing. And the ultimate goal can be maintained in prospective memory even though the subordinate goals might change.

Chapter 6 also suggests a key role for the dorsal PF cortex in developing an efficient strategy for sequential goals. Because most anthropoids forage in social groups, in which individuals compete vigorously for resources within a patch, an efficient plan for acquiring a selected set of fruits or leaves could provide an especially important advantage.

6. **Valuation.** If, during feeding, an animal approaches satiation on a particular food, this will decrease the subjective value of that food and the species of tree that produces it. When biological needs or priorities change in this way, foraging goals can change, too. Chapter 4 explains the advances that the granular OFC provides to primates in evaluating objects.

Summary

According to our proposal, the granular PF cortex of anthropoid primates provides them with a new capacity: the ability to use a single event to generate a goal. The learning system implemented by the granular PF cortex thus augments the ancestral reinforcement-learning system, which learns by slow and cumulative adjustment of associations. When faced with the kind of foraging problems that anthropoid primates encountered during their evolution—characterized by periods of dearth and attrition resulting from a reliance on specific products of angiosperm trees—the ancestral system inevitably produced a slew of errors. Errors are dangerous, and errors are costly. Both their new learning system and the ancestral one reduce errors and maximize rewards, but the primate PF cortex does so faster, which provides a crucial adaptive advantage.

Despite the contrast that we draw between the new and ancestral learning systems, our proposal does not imply that the PF cortex operates entirely independently of the latter. Chapters 3 and 4 propose that the agranular parts of the PF cortex play a key role in influencing habits and other conditioned behaviours. Nor should our proposals about foraging choices be taken to imply the absence of a comparable role in social choices.

Conclusions

Early primates

We propose that the granular PF cortex of early primates improved their ability to find and evaluate objects in the fine-branch niche. They could learn, based on a single experience, which choice among visual items produced a given outcome (Chapters 4) and they could maintain both overt and covert attention toward their goals (Chapter 5).

The development of granular PF areas came along with a suite of adaptations to the fine-branch niche. The shift to a hindlimb-dominated mode of locomotion freed the hands for a new feeding technique. Advances in stereoscopic vision began the process through which primates became, as they are often called, ‘visual animals’. New posterior parietal and inferior temporal areas also appeared in early primates, along with the premotor areas that make use of parietal inputs to guide reaching and grasping movements in a visual coordinate frame (Chapter 2).

In this context, the caudal PF cortex provided advantages in terms of overcoming clutter and interference in the fine-branch niche (Chapter 5). Likewise, the granular OFC improved the ability to choose among objects by contrasting the current biological value of various items in the fine-branch niche, predominantly based on vision and the linkage of particular choices with specific outcomes (Chapter 4).

Anthropoid primates

Additional granular PF areas appeared later, during the evolution of anthropoid primates, as these animals increased in size, ranged far in foraging, and came to depend on rich but volatile resources such as ripe fruits and immature leaves. They foraged by day in a competitive environment under a serious threat of predation. This kind of life placed a

premium on making good foraging choices, avoiding unproductive and costly ones, and learning to do so quickly based on limited experience.

The new granular areas of anthropoids included the dorsal and ventral PF cortex and probably the polar PF cortex, as well. These areas evolved along with visual advances such as foveal and trichromatic vision (Chapter 2). Their visual advances enabled these primates to attain a new level of sophistication in analysing the location, colour, shape, texture, glossiness, and translucence of items in their field of view. Their new prefrontal areas enabled them to generate a goal or sequence of goals based on a single event. To do so, they used sophisticated sensory contexts that included the places, timing, and order of visual events (Chapter 6), visual scenes (Chapter 3), and cues from both visual and acoustic signs (Chapter 7). These areas permitted evolving anthropoids to learn, based on a single experience, which goal in a visual scene to choose (Figures 3.10 and 8.4), which of two objects to choose as a goal (Figure 8.2), and which goal to choose in the context of an arbitrary sign (Figure 8.5).

According to the ideas advanced in this book, the prefrontal areas that evolved in anthropoid primates were a special-purpose adaptation, one that overcame a specific problem at a particular time and place in anthropoid history. These areas reduced the errors that these animals might otherwise have made during long-distance foraging excursions, in daylight, aimed at attaining capricious resources. The means by which anthropoids solved their specific foraging problem had profound consequences for later primate cognition, however. They solved their *specific* problem—periodic dearth of resources and attrition—by evolving a new *general-purpose* learning system, one that surmounted the limitations of the ancestral one. The ancestral general-purpose learning system, which slowly adjusts associations among stimuli, responses, and outcomes, produced too many errors.

The anthropoid way of learning has three key aspects. Through fast learning, the anthropoid PF cortex solves foraging problems very quickly, often based on a single experience. Through the learning and application of abstract rules and strategies, the primate PF cortex solves novel foraging problems by bringing to bear experience with similar situations. Through the attentive control of behaviour, anthropoid primates can surmount the ancestral learning mechanisms when they perform poorly, as they inevitably will during foraging crises.

We conclude that during two key periods in primate history the granular PF cortex provided our ancestors with a subtle adaptive edge, one specifically suited to their niches, problems, and opportunities. The subtlety of this edge explains why nonprimate mammals can get along so well without granular PF areas, as can primates with damage to them. Without their granular PF cortex, primates—like other mammals—rely instead on ancestral learning mechanisms.

This chapter proposes a simple function for the primate prefrontal cortex, mainly on the basis of studies in monkeys. It might seem that a function so fundamental could never explain the activations occur in the prefrontal cortex while people perform complex cognitive tasks. The next chapter therefore takes up the challenge of accounting for these activations.

Chapter 9

Human prefrontal cortex: generating goals from instructions and imagination

Overview

This chapter examines whether our proposal concerning the fundamental function of the PF cortex can account for the imaging activations that occur there when people perform complex cognitive tasks. Many activations in the human PF cortex seem to reflect elaborations of the context, goal, and outcome hierarchies, the generation of goals from contexts, the use of events and abstract rules to choose goals, or the prospective coding of goals. Some of these activations occur in areas that might have appeared during the evolution of apes or humans, and we try to account for these via the concept of re-representation. The expansion of existing PF areas, along with the possible appearance of new ones, led to changes in both the size and shape of the human brain, and changes in connections also occurred. We propose that the prefrontal cortex of modern humans and monkeys performs a common function inherited from their last common ancestor: it generates goals in a way that reduces errors. In a key advance, the human prefrontal cortex further reduces errors because people can learn from instruction or imitation and because people can engage in mental trial-and-error behaviour prior to any action. As a result—at least at times—humans can avoid errors altogether.

Introduction

Chapter 8 proposes that the PF cortex has a simple fundamental function. This chapter explores whether that function can account for the imaging activations seen in the human PF cortex while subjects perform complex cognitive tasks.

The reader will appreciate the difficulty of our undertaking. The proposal that we advance in Chapter 8 depends, for the most part, on data from monkeys. These data mostly concern choices among places and objects, as implemented with reaching or eye movements. To say that these functions are a far cry from analogical reasoning or making moral judgements is an understatement, to say the least.

The problem resembles the one faced by O'Keefe and Nadel (1978) when they first proposed that the hippocampus functions in navigation. It seemed a mystery at the time how a mechanism for navigation could also support episodic memory, although since then this combination has become less enigmatic (Burgess et al. 2002). We can now understand how the ancestral role of the hippocampus in navigation might have been elaborated during evolution to encompass a complex cognitive function like episodic memory. This chapter, likewise, attempts to account for activations on complex cognitive tasks in terms of an elaboration of ancestral mechanisms that evolved for making better foraging choices (Chapter 8).

There has been plenty of time for this elaboration. One only has to consider the fact that the last common ancestor of Old World monkeys and humans lived 23 or more million years ago (Ma) (Kay et al. 2004; Kumar et al. 2005). This fact means that the two lineages have been evolving separately for tens of millions of years, and during that time both human and monkey brains have surely changed. In this time, the human brain became ~4.8 times larger than one would expect for a monkey of the same body weight (MacLeod et al. 2003). At the same time, the human brain developed specializations of its own, which have been reviewed at book length (Passingham 2008).

This chapter begins with a brief summary of changes in the size and shape of the human brain during its evolution, with emphasis on the granular PF cortex. It then deals with connections and organization, including the possible appearance of new areas. The rest of the chapter addresses the key question: can the simple function that Chapter 8 advances for the anthropoid PF cortex account for the imaging activations that occur in the human PF cortex during advanced cognition?

The frontal lobes in hominid evolution

Genetic evidence suggests that apes diverged from the human lineage 5–7 Ma (Kumar et al. 2005), and the earliest fossil that might be a hominid, *Sahelanthropus tchadensis* (Guy et al. 2005), dates to approximately 7 Ma (Le Fur et al. 2009). This primate had a cranial capacity of ~360–370 cm³, about the same as a small chimpanzee (Guy et al. 2005). Modern human brains average around 1350–1550 cm³ (Sowell et al. 2007). Of course, people tend to be bigger than chimpanzees, but our brain is still 3.5 times larger than would be expected for a hypothetical ape of the same body size (MacLeod et al. 2003).

So hominid brains started small, at least by modern human standards. This history resembles the one that Chapter 2 lays out for anthropoid brains: a relatively small brain in relation to body size during its early evolutionary history, followed by a 'grade increase' in brain size during its later evolution.

Unfortunately, we cannot measure the size of the frontal lobes in fossil hominids. Unlike the fossil anthropoid brains that Chapter 2 describes, the thickness of the hominid dura mater prevents a clear impression of the sulci from forming on the inner surface of their skulls. So we can only comment on the overall shape of the brain. From this, we know that during hominid evolution the frontal lobes become wider and more rounded at the front.

Falk et al. (2000) made casts of the inner brain case in gracile and robust Australopithecines, early hominids that lived ~1.5–2.5 Ma. In the ‘robust’ Australopithecine, *Paranthropus*, the frontal lobes have a relatively pointed shape that resembles modern chimpanzees and gorillas. In the gracile Australopithecine, *A. africanus*, the frontal lobes have a slightly more rounded shape. We are lucky to have a very well preserved skull of a gracile australopithecine, *Australopithecus sediba*, from South Africa, dated ~2 Ma (Carlson et al. 2011). The shape of the orbital and polar PF cortex indicates a transition to the more rounded form seen in hominids of the genus *Homo*.

Bruner and Holloway (2010) measured the maximum width of the frontal lobes in Australopithecines and compared this result with the width in *Homo erectus* and *Homo neanderthalensis*, two hominids that evolved later. Relative to the maximum width of the inner brain case, the width of the frontal lobes in the more recent hominids exceeds that of australopithecines. This finding suggests an increase in the relative size of the frontal lobes during hominid evolution.

Modern humans probably evolved from a hominid related to *Homo heidelbergensis*, sometimes referred to as archaic humans. The Bodo skull from Ethiopia at 600 thousand years ago (Ka) and the Kabwe skull from Zambia at 300 Ka (Conroy et al. 2000) come from this species. Bookstein et al. (1999) have measured the slope of the front of the inner brain case in these skulls and compared it with that for two crania of early modern humans: the Omo I and Omo II skulls from Ethiopia, dated at 195 Ka (Day 1969). Although the archaic human skulls differ from those of early modern humans in having large brow ridges, the slope of the inner frontal brain case does not differ. This finding suggests that the shape of the frontal lobe reached a modern state in archaic humans, ~300–600 Ka. Of course, shape alone tells us little about the PF cortex, but these findings suggest that its shape stabilized relatively early in our recent evolution.

The findings imply that the frontal lobes were well developed some time before one of the key technological revolutions occurred in early modern humans. On the evidence of blade technology and bone tools, McBrearty and Brooks (2000) suggested that these developments occurred ~100 Ka, but they do not seem to have become well established until much later (d’Errico & Stringer 2011).

Relatives of these people dispersed from Africa 60–80 Ka (Mellars 2006), and genetic evidence shows that all Asians and Europeans have descended from them. These ancestors displaced the Neanderthals, created yet more specialized toolkits, and adapted to nearly every environment in the world.

PF cortex size in modern primates

One can only gain hints about the evolution of the frontal lobes from fossils, because shape and size tell us so little about the organization or function of the PF cortex. And, of course, the granular PF cortex makes up only a part of the frontal lobes.

Chapter 2 explains that the increase in brain size during anthropoid evolution accompanied the generation of new granular PF areas, specifically the ventral, dorsal, and polar PF cortex. Something of the sort also could have happened during human evolution, and

studying the granular PF cortex in living primates can yield some insight into this possibility. Unfortunately, despite the intensive attention devoted to human brain evolution, the literature comparing human brains with those of other primates does not support conclusions as reliably as those that we review in Chapter 2 for anthropoid primates. Nevertheless, it does support some tentative suggestions.

Brodmann (1912) estimated the surface area of the granular PF cortex and related it to that of the neocortex as a whole. The granular PF cortex, as Brodmann saw it, is ~11% of the neocortex in macaque monkeys, ~17% in chimpanzees, and ~28% in humans (see Figure 2.6).

These differences are very large. If Brodmann's data are correct, the PF cortex averages 34,770 mm² humans compared with 6719 mm² in chimpanzees. This makes it ~5-fold larger in humans, even though a typical person weighs only 10–20 kg more than a chimpanzee. The difference is even more striking when one considers that the primary motor cortex (area 4) is little different in size in humans and chimpanzees (Preuss 2011).

Semendeferi et al. (2002) have disputed Brodmann's estimates for chimpanzees. They estimated the percentage of the frontal cortex that lies rostral to the precentral sulcus in great apes, 26–30%, and found that it differs only a little from the corresponding percentage in humans, 29–33%. But, as they acknowledge, there is a difference between estimating the percentage of cortex that lies rostral to the precentral sulcus and estimating the percentage of granular PF cortex.

Passingham (2008) has pointed out that Bailey et al. (1950) considered some of the cortex rostral to the precentral sulcus in chimpanzees, area FC, to be dysgranular rather than granular. It is clear from the map of the chimpanzee brain in Brodmann (1912) that he might have excluded this region from his measurement of the granular PF cortex. And this factor might account, in part, between the estimates given by Semendeferi et al. and Brodmann.

Elston et al. (2006) used Brodmann's data to estimate the percentage of the frontal lobe occupied by the granular PF cortex. They found that the granular PF cortex makes up ~80% of the frontal lobe in humans, 55% of the frontal lobe in chimpanzees, 53% in gibbons, 45–50% in catarrhine (Old World) monkeys, 41–46% in platyrhine (New World) monkeys, and 41–43% in strepsirrhine primates (see Figure 2.6E). These findings suggest that the granular PF cortex expanded considerably during human evolution.

A recent analysis of gene expression yields some important insights into how human brains became so large during evolution and how they do so during fetal development. Zhang et al. (2011) examined the locations and degree of transcription for genes that evolved in primates after the divergence of primates and rodents. Figure 2.8 illustrates this split in the form of a cladogram. They called genes that evolved after this split *new* genes, as opposed to the *old* genes inherited from the last common ancestor of primates and rodents. Compared to mouse brains, Zhang et al. found enhanced transcription of new genes in developing human brains, most of which occurred in the neocortex. The young genes encoded many transcription factors, which control the pattern and rate of development. They also showed evidence of changing the amino acids that they encoded

faster than did the old genes. Zhang et al. concluded that factors selecting for some aspect of brain function contributed to the origin of the young genes. For the present purpose, we find of most interest their finding that, amongst neocortical areas, the transcription of many human-specific genes occurred specifically in the PF cortex.

So far, we have discussed the shape of the frontal lobe as a whole and the size of granular PF cortex, also as a whole. But these data cannot tell us about particular areas. The polar PF cortex is among the areas that probably first appeared in anthropoids (Chapter 2). It is small in anthropoid monkeys, but it has become the largest of the cytoarchitectonic areas in the human frontal lobe (Öngür et al. 2003). In all likelihood, the expansion of the polar PF cortex during hominid evolution led to the shape changes mentioned earlier. The rounding and broadening of the rostral frontal skull in archaic humans probably means that the expansion of the polar PF cortex reached its modern state 300–600 Ka.

Semendeferi et al. (2001) estimated the extent of the polar PF cortex (area 10) in modern apes and humans. Relative to the brain as a whole, the polar PF cortex forms roughly twice the percentage of the brain in humans compared with chimpanzees (Figure 9.1).

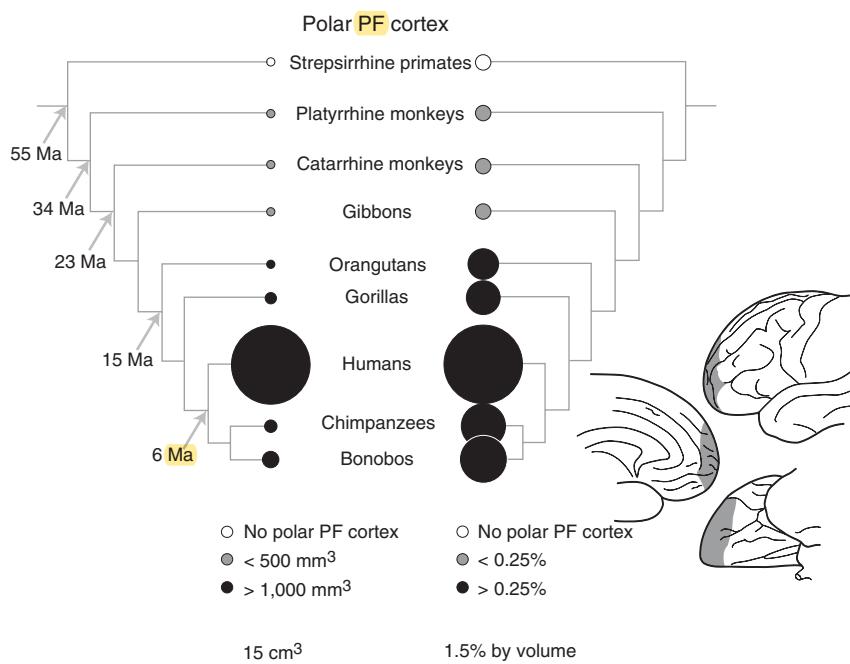


Fig. 9.1 Expansion of the polar PF cortex (area 10) in humans. Cladogram for selected primates with approximate divergence times on the left (arrows) in millions of years (Ma). The diameter of each circle encodes a size parameter for the polar PF cortex, given by the scale at the bottom, classified by the greyscale code shown below each cladogram. The inset shows the location of the polar PF cortex in humans. Left, medial view with rostral to the right and dorsal up; top right, lateral view with rostral to the left and dorsal up; bottom right, ventral view with rostral to the left and lateral up. Modified from Tsujimoto S, Genovesio A, Wise SP. *Trends in Cognitive Sciences* 15:169–76, © 2011, with permission from Elsevier.

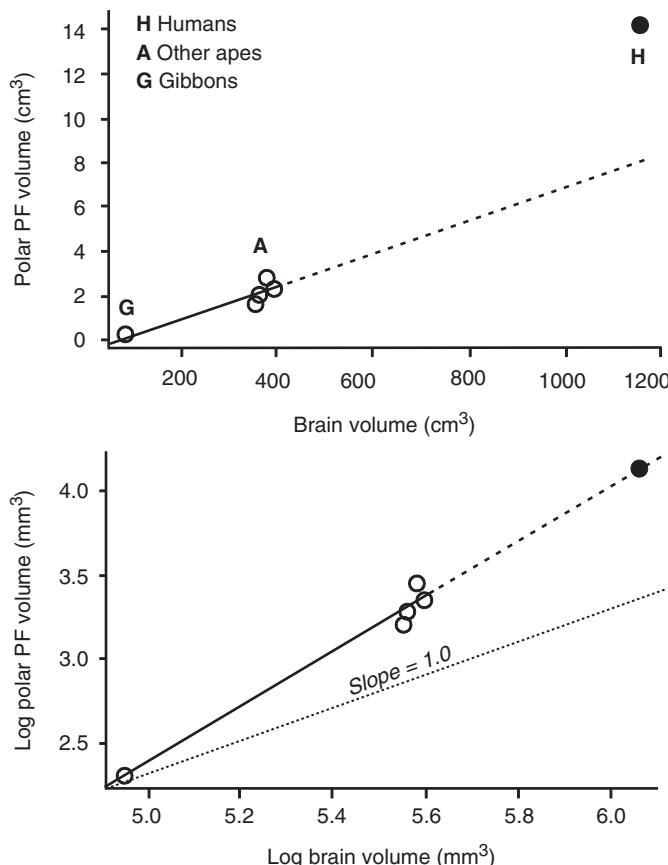


Fig. 9.2. Regressions of the volume of polar PF cortex as a function of brain volume in selected groups of primates. Solid line: regressions from the ape data; dashed line: extrapolation to a brain the size of that in humans. Top: Linear scale. Bottom: Log-log scale, with unity slope indicated by the dotted line. Abbreviations: G, gibbons; A, great apes; H, humans. Modified from Semendeferi K, Armstrong E, Schleicher A, Zilles K, Van Hoesen GW. Prefrontal cortex in humans and apes: a comparative study of area 10. *American Journal of Physical Anthropology* 114:224–41, © 2001, John Wiley and Sons.

The same authors performed a similar analysis on area 13 and found no such expansion in humans compared to other great apes. These findings support the conclusion that the polar PF cortex expanded markedly during human evolution.

However, Holloway (2002) has downplayed these results. He pointed out that the size of the polar PF cortex in the human brain is only 6% larger than predicted for an ape with a brain as large as the human brain. Figure 9.2 shows the log-log regression for the size of the polar PF cortex versus brain size in apes (Semendeferi et al. 2001), and it shows that the human value lies only just above the regression line.

But Holloway (2002) assumed that if the human polar PF cortex fits the log-log regression line, or nearly so, then it has an equal capacity. This belief neglects the fact that the

log-log regression line has a slope of 1.6, which greatly exceeds unity slope (1.0). The steep slope means that larger brains have a greater *proportion* of polar PF cortex than do smaller brains. So we cannot assume a similar capacity.

An example from outside the neurosciences explains this point (Gould 1973). The extinct Irish elk had enormous antlers, but their length fell near a regression line when plotted against a measure of body size: shoulder height. Because the slope exceeded unity, their antlers made up a greater proportion of their body. And they therefore functioned more effectively, presumably in attracting mates. Thus the fact that a structure fits a regression line does not imply equivalent functional capacity.

Summary

The human brain is not simply a scaled-up version of the brain that the last common ancestor of macaque monkeys and humans had. Some parts of the brain have expanded more than others. When considered as a proportion of the neocortex as a whole, the granular PF cortex is ~2.5 larger in humans than in macaque monkeys.

However, size tells us only a little, so we next consider differences in microstructure and internal connections between human and other brains.

Microstructure and internal connections

In their study of the polar PF cortex, Semendeferi et al. (2010) found that in this area there was a large amount of neuropil between cell bodies in layer 3 in humans compared to apes. In other words, the cell bodies are more widely spaced. This anatomical feature presumably reflects a greater number of dendrites, dendritic spines, and terminals in humans compared to apes. This trait points to an elaboration of the integrative function of the granular PF cortex, in general, and of the polar PF cortex, in particular.

Elston (2001) measured the number of spines on the dendrites on the layer 3 pyramidal cells in the PF cortex. He found that these cells were 70% more spinous in the human than in the macaque monkey brain. Because the connections terminate on spines, this finding implies that each cell can integrate more information in the human PF cortex compared with the macaque monkeys.

Elston (2007) also plotted the number of spines against the size of the PF cortex in a variety of primates, including humans. He found that the larger the PF cortex, the greater the number of dendritic spines. Given the large size of the human PF cortex, the number of spines matches expectations closely. This does not seem to be an artefact of the increase in cell size.

Intrinsic connections run in the subcortical white matter, and they come in two types. Schenker et al. (2005) distinguished between the long association fibres that lie in the core of the white matter and the shorter fibres that connect neighbouring regions within the gyri of the PF cortex. They compared these values for a selection of primates. In humans, the volume of the white matter that contains the long association fibres was as predicted for a brain of human size. However, the short fibres were more extensive than expected in humans.

Summary

In Chapter 8 we review evidence that the proportion of spines increases as one ascends the various processing hierarchies for context, goals, and outcomes. We argued that this anatomical feature allowed the brain to form representations at an increasingly abstract level. The human PF cortex can take this development to a new level. In addition, the human PF cortex seems to have a larger volume of short fibres that connect one PF area to another. Thus the human PF cortex may be particularly well equipped to integrate information. In later sections we present evidence that some of the activations in the PF cortex reflect the ability to integrate information from different cognitive domains.

External connections

The previous section considered the number of connections, but not the overall pattern of the long-range connections. Recent research has taken advantage of the fact that water diffuses along axons both externally and internally (Basser & Ozarslan 2009). This property has led to a method for studying connections in the human brain called diffusion tensor imaging (DTI). Schmahmann et al. (2007) used a modification of this method to chart the connections in monkeys and found results like those for standard axonal fibre-tracing methods. However, DTI has serious limitations. These methods will never have the sensitivity of methods in monkeys and other animals that can reveal connections at the microscopic level and, where sufficiently important, at an electron-microscopic level. They cannot reveal the exact origin and termination of projections, as the methods used in monkeys can. Nevertheless, DTI data have provided valuable information about connections in the PF cortex of humans.

Croxson et al. (2005) divided the PF cortex into seven sectors: dorsal PF, ventral PF, lateral orbital PF, central orbital PF, medial orbital PF, anterior cingulate gyrus, and cingulate sulcus. They measured the likelihood that a seed area connects with another region, using a method devised by Hubbard et al. (2005), and found that the general pattern of the connections of the PF cortex in humans resembles that in monkeys. For example, the posterior parietal cortex connects with the dorsal PF cortex, and the inferior temporal cortex connects with the ventral and orbital PF cortex. In both monkey and human brains, the amygdala connects with the orbital PF cortex and the anterior cingulate cortex.

The same group of investigators used DTI to divide the anterior cingulate cortex into nine regions (Beckmann et al. 2009). The results for the human brain resembled those from axonal fibre-tracing studies in monkeys (Carmichael & Price 1996). For example, in the medial PF cortex, the pregenual and subgenual areas have the strongest connections with the orbital PF cortex, amygdala, hypothalamus, and ventral striatum in both species.

DTI has also shown that the overall pattern of connections between the mediodorsal nucleus of the thalamus (MD) and the PF cortex is similar in humans and monkeys (Klein et al. 2010). The medial part of MD connects with the orbital PF cortex, caudodorsal MD with the medial PF cortex, including the anterior cingulate cortex, and lateral MD with the dorsal PF cortex.

Summary

The overall pattern of the connections of the PF cortex seems similar in humans and macaque monkeys, as far as we can tell. This similarity presumably reflects descent from our last common ancestor. However, modern macaques and humans have been evolving separately for 20–30 million years, and this means that specializations could have developed in either lineage. In the next sections, we point to three possible specializations of the human brain: Broca's area, the lateral part of the polar PF cortex, and the dorsal paracingulate cortex.

Broca's area

Broca's area, Brodmann's areas 44 and 45, lies in front of the ventral premotor cortex (area 6). From caudal to rostral, the ventral premotor cortex is agranular, area 44 is dysgranular, and area 45 is granular (Petrides et al. 2005). The same progression can be found in monkeys (Figure 9.3) in a topologically comparable region.

Klein et al. (2007) used DTI to chart the overall pattern of connections of areas 44 and 45 in the human brain. They concluded that areas 44 and 45, as distinguished by their connections, corresponded well with areas 44 and 45 as defined by cytoarchitecture (Figure 9.3). DTI data show that in the human brain area 44 connects with the inferior parietal cortex and area 45 connects with the temporal cortex (Frey et al. 2008). And Croxson et al. (2005) found the same pattern of results using DTI in monkeys, as did Petrides and Pandya (2009) using standard tracers.

Rilling et al. (2008) used this finding as a starting point to compare the Broca's area in humans, chimpanzees, and monkeys. They found that area 45 has stronger connections

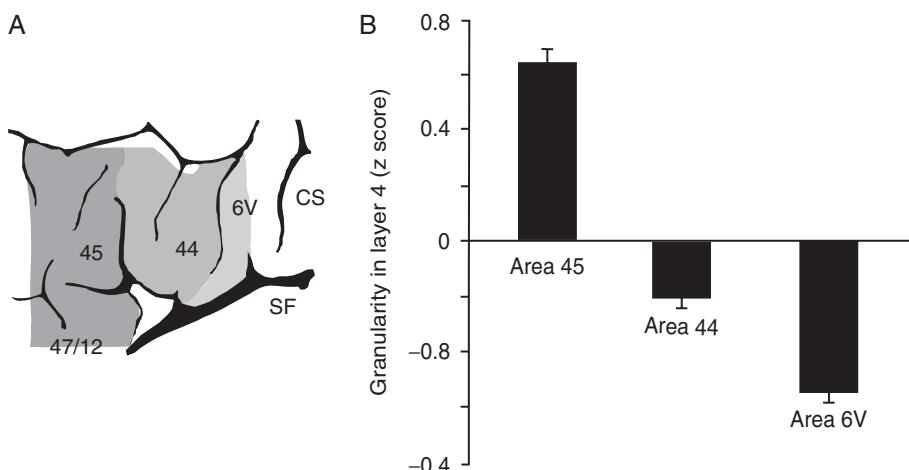


Fig. 9.3 (A) Broca's area in the human brain. Abbreviations: CS, central sulcus; SF, Sylvian fissure; 6V, ventral area 6. (B) Density of layer 4 in monkeys relative to the mean in the same three frontal areas. Reprinted by permission from Macmillan Publishers Ltd. Petrides M, Cadoret G, Mackey S. Orofacial somatomotor responses in the macaque monkey homologue of Broca's area. *Nature* 435:1235-8, © 2005, Nature Publishing Group.

with the middle temporal cortex than does area 44. Rilling et al. then compared chimpanzees and humans and found that the middle temporal cortex has more widespread connections with Broca's area in humans than in chimpanzees. Finally, in humans this pathway is larger and more widespread in the left hemisphere than in the right, whereas in chimpanzees it is symmetrical. As children develop, the strength of these connections increases in the left hemisphere, but not in the right (Paus et al. 1999).

Summary

The idea that Broca's area evolved on the left side of the human PF cortex is certainly nothing new, but imaging activations have supported this idea. People can hold articulations in memory (Conrad 1972) and can reason about words (Goel & Dolan 2004). When they do so, imaging activations tend to be in the left hemisphere. But when they process visuospatial information, the activations tend to be in the right hemisphere (Smith et al. 1996). Although the comparative evidence reviewed here remains far from conclusive, it seems broadly consistent with the language specializations that have been observed in the human brain.

Polar PF cortex

The studies of Broca's area suggest a change in connectivity in humans compared to the last common ancestor of humans and chimpanzees. In addition, the literature contains suggestive evidence that two areas in the human brain lack homologues in monkeys: the lateral part of the polar PF cortex, part of area 10, and the dorsal paracingulate cortex, part of area 32.

Semendeferi et al. (2001) suggested that the lateral part of polar PF cortex exists in great apes and humans, but not in monkeys. If accepted, this idea would imply that it evolved in the ancestor of great apes and humans. Their conclusion, however, depended solely on topological and cytoarchitectonic evidence. Given that the latter depended on subjective criteria, more evidence is needed to accept this idea, although it seems plausible.

Nelson et al. (2010) found supporting evidence in the form of a correlation between activation in the centre of the inferior posterior parietal cortex and activation in the lateral polar PF cortex. Mars et al. (2011) compared resting-state correlations in humans and monkeys. They selected a region of interest on the border between the mid-lateral PF cortex and the polar PF cortex. In humans, resting activation of this area correlated with activations in a central part of the inferior parietal cortex, in agreement with the findings of Nelson et al. But Mars et al. did not find a corresponding correlation in monkeys, and this finding agrees with the absence of a connection between the two areas in axonal transport studies (Petrides & Pandya 2007). These findings are consistent with the suggestion that the lateral polar PF cortex (area 10), or the region adjacent to it, evolved after the monkey–ape split. However, further evidence is needed on this possibility.

If the lateral part of the polar PF cortex evolved in humans and apes, then this area could be regarded as lying at the top of a processing hierarchy. Summerfield and Koechlin (2009) have proposed a caudal-to-rostral hierarchy for the lateral PF cortex, which they

relate to the complexity of the contexts that specify action. And Koechlin et al. (1999) has suggested that the most rostral part, lateral area 10, holds primary goals in mind while processing secondary ones.

Summary

A limited amount of evidence supports the idea that the lateral part of the polar PF cortex (area 10) occurs in humans and ape brains, but not in monkey brains. It might create a new level in a caudal-to-rostral hierarchy within the lateral aspect of the granular PF cortex.

Dorsal paracingulate cortex

In human brains that have a paracingulate sulcus, the dorsal paracingulate part of area 32 lies between the cingulate sulcus and the paracingulate sulcus (Vogt 2009). A paracingulate sulcus can also be seen in some chimpanzee brains, and the cortex between this sulcus and the cingulate sulcus might correspond to the dorsal paracingulate cortex of humans. We need more evidence to tell.

Monkeys also have an area called area 32 (Vogt 2009), but its cytoarchitecture suggests that it is homologous with the pregenual medial PF cortex in humans and not with the dorsal paracingulate cortex. DTI studies also provide evidence that the dorsal paracingulate cortex is present in humans but not in monkeys. The pregenual medial PF cortex has connections with the amygdala and the hypothalamus in both humans and monkeys, but the dorsal paracingulate cortex lacks such connections (Beckmann et al. 2009). The dorsal paracingulate cortex does, however, connect with the dorsal PF cortex, and a meta-analysis by Koski and Paus (2000) led to the conclusion that activations in the dorsal paracingulate cortex tend to correlate with activations in dorsal PF. These data provide suggestive evidence that the dorsal paracingulate cortex evolved after the monkey–ape split.

Summary

If the dorsal paracingulate cortex exists only in humans and apes, it might, like the polar PF cortex, contribute an additional level to a caudal-to-rostral hierarchy within the PF cortex. For the polar PF cortex this hierarchy involves the lateral PF cortex, but for the dorsal paracingulate cortex, it involves the medial PF cortex. Others have suggested this kind of hierarchy (Amadio & Frith 2006; Summerfield & Koechlin 2009), and we present evidence later that supports this idea (see Figure 9.7). There we propose that these hierarchies, for both the lateral and medial PF cortex, involve the re-representation at higher levels of information that its lower levels process.

We do not mean to imply that the three areas emphasized here were the only ones to appear during the evolution of apes or humans. Some evidence, based on the degree of cortical myelination, indicates that a small part of area 47, a component of the ventral PF cortex called area 47m, might also have appeared in the ape–human lineage (Glasser et al. 2011). Evidence from the same study also supports the idea that the granular PF cortex,

which is sparsely myelinated, expanded dramatically during the evolution of apes and humans.

Activations in the human brain

If we accept that the PF cortex differs in monkeys and humans, then we should expect that its function differs, as well. After all, modern monkeys and humans have been evolving separately for 20–30 million years, and they have travelled a very different path. Yet monkeys and humans share a common ancestor, and Chapter 2 explains something about those animals. In Chapter 8, we proposed a fundamental function of the PF cortex as extinct anthropoids evolved it, and as modern monkeys have inherited it. So in the remainder of this chapter we explore whether some uniquely human functions of the PF cortex might be understood as elaborations of the fundamental function that evolved in our common ancestors.

In the sections that follow we consider the imaging activations that have influenced the views of cognitive psychologists concerning the function of the PF cortex in the human brain. In many cases, we suggest how the activation might be explained on the basis of the proposal that we put forward in Chapter 8. In some cases, when we cannot do that in a straightforward way, we suggest ways in which the proposal function may have been elaborated during human evolution.

For clarity of exposition, we list the activations that we consider in a set of tables. At the beginning of each section, we present a table of the activations to be considered in that section. We have organized the tables by relating the activations to the context, goal, and outcome hierarchies (Tables 9.1–9.5) that allow the PF cortex to map contexts to goals (Table 9.6). The last three tables relate to the generation of goals on the basis of events (Table 9.7) and abstract rules (Tables 9.8 and 9.9).

Sensory processing

We proposed that the granular PF cortex generates goals according to the current context, and that it can do so because it lies at the top of the context hierarchy. Table 9.1 therefore lists activations that relate to the processing of the context.

Sensory decisions

If the current goal depends on the context, then it is necessary to identify that context. In many instances sensory inputs provide an unambiguous and strong signal conveying a

Table 9.1 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Context	Sensory decisions	Identifying the context
	Sensory imagery	Generating a sensory context
	Sensory awareness	Re-representing a sensory context

current context, but often these inputs are less clear. In such cases, the subject must make a perceptual decision. As explained in Chapter 3, we follow Schall (2001) in distinguishing perceptual decisions about the world from choices among goals and choices among actions.

Heekeren et al. (2006) presented a display of moving dots, and the subjects had to decide whether the dots moved in the leftwards or rightwards direction. The experimenters manipulated task difficulty by varying the proportion of dots that moved in the same direction, that is, coherently. In order to identify activations that might be related to perceptual decisions, as opposed to choices or responses, Heekeren et al. introduced two conditions. In one, the subjects reported their decision by making a saccade to the left or right, and in the other they did so by pressing a button on the left or right. Heekeren et al. looked for activations that were the same for these two reporting conditions.

Heekeren et al. found activations that fulfilled this requirement in the dorsal PF cortex and in the polar PF cortex, as well as in the posterior parietal cortex. In a previous study (Heekeren et al. 2004), the same authors found an activation in the dorsal PF cortex when subjects had to decide whether a degraded image was a house or a face.

Heekeren et al. (2006) suggested that their results differed importantly from those obtained with monkeys. Their claim was that activations in the PF cortex of humans reflect decisions or perceptions, whereas the activity in the PF cortex of monkeys reflects planned actions or visuomotor associations. They assumed that when monkeys make a saccade to report the direction of moving dots, PF cell activity encodes the appropriate saccade (Kim & Shadlen 1999).

Notwithstanding their conclusion, the results for humans and monkeys are completely compatible. Gold and Shadlen (2007) used microstimulation of the FEF after training monkeys to report the direction of coherent dot movement by making a saccade to a red or green target. The monkeys did not know in advance on which side each target would appear, and so could not prepare a saccade. Stimulation affected the choice of goal, and not the direction of the saccade. Thus, activity in the caudal PF cortex reflects the goal rather than the action that the monkey performs to achieve it. And the activations reported by Heekeren could be explained in the same way: they could reflect the goal (left, for example), irrespective of whether the subject presses the left button or makes a saccade to the left.

Another problem with the conclusions of Heekeren et al. is that treated voxels as if they were cells. Chapter 1 explains the dangers in making such an assumption. Given that each voxel contains many thousands of cells, and that the BOLD signal reflects synaptic rather than cell activity, it is more likely that some cells within a voxel encode a perceptual decision and others encode a goal generated on the basis of that decision. In a study on monkeys, Lebedev et al. (2001) found cells in the PF cortex of monkeys that reflected their report of the direction of illusory movement, and these cells showed similar activity irrespective of the direction of the saccade that the monkeys use to make that report. But the subpopulation of cells that showed this property was intermixed with cells encoding saccades directly to a visible goal. An imaging experiment could not sort out these intermingled populations of cells and the synaptic inputs that drive activity.

Lebedev et al. concluded that the PF cortex is in a position to integrate perceptual information, which corresponds to the current context, with the choice of a goal generated on the basis of that context. We see no reason to interpret the imaging activations in human subjects any differently. Thus the results of the studies by Heekeren et al. agree with the proposal that we make in Chapter 8. We suggested that the PF cortex lies at the top of the context hierarchy, and this means that it can identify the current context and generate the appropriate goal. Humans can contemplate these contexts without generating any goal, and much of the mental life of our species is devoted to doing so. This capacity does not, however, indicate any fundamental difference between the PF cortex in humans and monkeys.

Sensory imagery

People can not only make decisions about stimuli such as faces and houses, they can also imagine such stimuli. And when they do so, activation occurs in the mid-lateral PF cortex (Ishai et al. 2000) and in the ventral PF cortex (Ishai et al. 2002). Yet, when subjects simply see faces and houses, little PF activation occurs. Hassabis et al. (2007a) specifically compared the memory for observed and imagined objects. The ventral PF cortex showed increased activation for imagining both familiar and novel objects.

Imagining faces and houses also activates the temporal lobe. And just as the locations of the activations differ when subjects see faces or houses, so they differ when the subjects imagine them (Ishai et al. 2000). To test whether such activations depend on top-down influences from the PF cortex or, alternatively, on the posterior parietal cortex, Mechelli et al. (2004) used a statistical method that allowed them to analyse the influence on one area on another. They examined cortical interactions during imagery for faces, houses, and chairs. The granular PF cortex interacted with different parts of the temporal lobe depending on the content of the imagery, but activations in the posterior parietal cortex did not. This finding agrees with the idea that the PF cortex generates imaginary contexts.

Generating images reflects the fundamental function of the PF cortex in two ways. First, the representation of an image resembles a current context, especially one stored in memory. Second, as Chapter 8 explains, the granular PF cortex becomes engaged in attention demanding, as opposed to automatic, control of behaviour, and imagery requires attention.

A dual-task paradigm used by Bruyer and Scailquin (1998) illuminates this point. They required subjects to imagine letters in a place and later asked whether a probe appeared at the same place (Kosslyn et al. 1995). When the subjects had to generate random numbers at the same time, thus compelling attentive control, they made many errors in generating the image. Once they had generated the imaginary letters, however, subjects could maintain them in memory without interference from the random-number task. Thus generating an image requires attentive control and the engagement of the PF cortex.

In later sections, we discuss other tasks which require subjects to generate representations. For example, the ventral PF cortex becomes activated when subjects generate verbs from nouns. When presented with 'cake' the subject might generate 'eat' or 'cut'. However,

no significant activation occurs when experimenters present the same list of nouns repeatedly and subjects make stereotyped responses to them (Raichle et al. 1994). These results support the claim that the attentive generation of context representations depends on the PF cortex and thus accounts for the activations observed in such tasks.

Sensory awareness

Given that the PF cortex lies at the apex of the context hierarchy, it has been suggested that it may be essential for the awareness of sensory stimuli (Crick & Koch 1998). And many imaging studies compare conditions with and without awareness (Rees et al. 2002). One such example concerns change blindness. Beck et al. (2001) presented letters centrally and required subjects to perform a letter detection task. Pictures appeared peripherally, and on some occasions they changed from one display to the next. The experimenters varied the difficulty of the letter task so that on some trials the subjects noticed the change in the periphery but on other trials they did not. Awareness correlated with activations in the postero-lateral and caudal PF cortex and in the posterior parietal cortex.

Backward masking can also prevent awareness. In this procedure, one stimulus rapidly follows another. For short intervals between the two stimuli, 30 ms or so, the second stimulus can block awareness of the first. Lau and Passingham (2006) used this technique, and they adjusted the timing of the two stimuli in order to equate the percentage of trials on which the subjects did or did not detect the first stimulus in two conditions. The subjects had to say whether the target stimulus was a square or a diamond, and the two conditions were matched for the accuracy with which the subjects could do this. However, the conditions differed in the percentage of trials on which the subjects said that they had 'seen' the stimulus. On some correct trials, subjects felt they had been guessing, albeit correctly. More activation occurred in the mid-lateral PF cortex when the subjects judged that they had 'seen' the stimulus than when they simply 'guessed' that they had seen it.

If the PF cortex is necessary for sensory awareness, a PF lesion should interfere with awareness. So in a subsequent study Rounis et al. (2010) applied repetitive transcranial magnetic brain stimulation (rTMS) bilaterally to the PF cortex just before the subjects performed the backward-masking task. They stimulated at the theta frequency in order to depress activity in the affected area; then they tested the subjects (Huang et al. 2005). The temporary inactivation had no effect on the accuracy with which the subjects judged the identity of the target stimulus. However, it did affect the percentage of trials in which the subjects reported that they had 'seen' the stimulus.

Del Cul et al. (2009) also used backward masking and tested patients with frontal cortex lesions for their ability to detect digits. The authors matched performance for the patients and controls by delaying the masking stimulus for longer after the target stimulus in the patients than in the controls. As expected from the studies just mentioned, the patients with PF cortex lesions said that they had 'seen' the digits less frequently than did healthy subjects, especially when lesions included the left polar PF cortex. Thus activation in the PF cortex seems to relate to a *reflective* awareness, which refers to the confidence of a person that they have seen something.

Summary

Chapter 8 suggests that the PF cortex lies at the top of a context hierarchy. It also argued that as one ascends this hierarchy, higher levels re-represent information that lower levels process, and they often do so in a more abstract form. Because the PF cortex lies at the top of the context hierarchy, it can re-represent a person's perceptual judgements and make decisions concerning those judgements. The addition of a new level to the context hierarchy might underlie this function, a topic that we return to later.

Generation of goals

Chapter 8 emphasizes concrete goals such as objects or locations. But humans generate a rich variety of goals. Sometimes a word can be a goal, such as when one searches memory for a word. So Table 9.2 expands the notion of a goal as we have used it so far.

Verb generation

In an early paper, Petersen et al. (1988) used positron emission tomography (PET) to record activations when people generate verbs that are appropriate to particular nouns. It was up to the person which verb to generate. So, given the noun 'cake', they might say 'eat', 'cut', or 'make'. In the comparison condition, the subjects simply repeated the noun.

When Petersen et al. compared these two conditions, more activation occurred in the PF cortex when the subjects generated verbs. A subsequent study showed that the peak of the activation was found in the ventral PF cortex (Buckner et al. 1995). As already mentioned, when subjects saw the same list of nouns repeatedly, they tended to produce the same verb in response to a particular noun (Raichle et al. 1994). And when their choices had become stereotyped in this way, the activation in the PF cortex no longer exceeded that in the control condition.

These results show that the PF activation reflects the attentive generation of goal items, in this case a verb that was appropriate to a given noun. However, the findings of Petersen et al. have another important implication. In verb generation, the noun provides the current context, and the activation therefore could also reflect the generation of the goal that was appropriate for that context.

Experimenters can present many kinds of contexts. For example, Nathaniel-James and Frith (2002) presented incomplete sentences, and the subjects had to supply the final word. In one condition, the sentence constrained the word. For example, subjects might

Table 9.2 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Goals	Verb generation	Generating goal items according to context
	Imagine actions	Generating goals appropriate to the context
	Planning	Generating a sequence of goals

have seen ‘he mailed the letter without a ...’, which constrains most people to generate ‘stamp’. The contrasting condition provided little constraint. When subjects saw a sentence like ‘the police had never seen a man so ...’, they could generate many words such as ‘drunk’, ‘evil’, and so on. Nathaniel-James found activation in the mid-lateral PF cortex in the unconstrained condition, contrasted with the constrained one.

These activations follow from the function that Chapter 8 proposes because the tasks involve the attentive generation of goals that are appropriate to the context.

Imagining actions

In an earlier section, we reviewed activations that relate to the ‘internal’ generation of visual images. But people can also imagine actions. For example, Gerardin et al. (2000) required subjects to make either simple finger movements or more complex ones. In neither case did any activation occur in the PF cortex. However, when the subjects had to imagine performing the same movements, the granular PF cortex showed significant activation. Ehrsson et al. (2003) later confirmed this result.

Motor imagery tasks typically lead to activations outside the PF cortex, as well. The tasks of Gerardin et al. and of Ehrsson et al. led to activations in the rostral premotor cortex and in the posterior parietal cortex. Such results are unsurprising because motor imagery may well involve the preparation of movements (Jeannerod 2006) and both the premotor and posterior parietal cortex become activated when subjects prepare movements (Toni et al. 2002).

Rather than requiring subjects to imagine movements, Rowe et al. (2002a) instructed them to think about their upcoming movements without imagining them. As in the studies of visual imagery, explained earlier, the key issue involved a hierarchy among three areas, which always included the PF cortex and the posterior parietal cortex. For visual imagery, the third area was the inferior temporal cortex; for motor imagery, it was the premotor cortex. Like the results for visual imagery, the analysis of Rowe et al. suggested that the key influence on the third area came from the PF cortex and not from the posterior parietal cortex.

The critical factor in this result involves attention. When motor preparation makes demands on attention, the PF cortex becomes activated. Rowe et al. found activation in PF cortex only when the subjects had to attend to the next goal. When they had to carry out a visual search task while performing a sequence of movements, thus diverting attention, the influence of the PF cortex on the premotor cortex decreased.

Like sensory imagery, imagining an action involves the attentive generation of a representation. In the case of sensory imagery, this representation relates to contexts; in the case of motor imagery, it relates to actions. We argue in Chapter 8 that, unlike the posterior parietal cortex, the PF cortex can generate these representations because it lies at the top of both the context and goal hierarchies.

Planning

People can also imagine a sequence of goals. In the laboratory, psychologists have assessed such planning through tasks that require a series of steps to reach a solution. For example,

on the Tower of Hanoi task, the subjects have to rearrange coloured rings in order to achieve a given target arrangement in the minimum number of steps. A simplified version, called the Tower of London task, uses three sticks and three coloured balls (Shallice 1982). Problems might require two, three, four, or five steps.

Dagher et al. (1999) found activation in the mid-lateral PF cortex when subjects performed the Tower of London task, along with greater activation in the polar PF cortex as the solution required a larger number of steps. Similar activations occurred whether the subjects merely plan the steps or both plan and execute them (Rowe et al. 2001; Unterrainer et al. 2005).

Although these areas are activated during planning, this finding does not show what processes these activations reflect. For example, we know that the more difficult problems involve counter-intuitive moves, such as the movement of the disc or ball away from its final destination (Goel & Grafman 1995). And Goel and Grafman (1995) have shown that patients with frontal lesions tend to make errors when moves of this sort are required.

There is, however, another concern, which is that the activations may relate to problem solving as opposed to planning per se. Some tasks, like the Tower of Hanoi, require both problem solving and planning. In daily life, people plan sequences of goals that do not require much problem solving, such as shopping trips. So Shallice and Burgess (1991) sent three patients with large frontal lesions on a series of errands in a shopping mall. These errands included, for example, buying a loaf of bread, and the experimenters instructed the patients not to go into the same shop twice.

Unfortunately, the lesion of only one of these patients has been described, and this large lesion involved the frontal pole and rostral orbital surface (Shallice & Cooper 2011). So Tranel et al. (2007) repeated the study with a large series of patients and described their lesions based on structural imaging. The patients that performed inefficiently had bilateral lesions that included not only a large part of the ventral and medial aspects of the frontal lobe but also the polar PF cortex.

Of course, one cannot perform imaging experiments on subjects while they perform errands. But one could do so if the subjects were simply asked to describe the series of steps needed to shop for groceries, for example. Godbout and Doyon (1995) asked subjects to generate scripts of this sort, and they found that patients with frontal lesions generated fewer steps and made more sequence errors.

Summary

Just as people can generate visual images, so they can imagine actions. This enables them to plan, and to do so far into the future. When people plan moves on the Tower of London task, the activation extends into the lateral part of the polar PF cortex for the more difficult the problems (Dagher et al. 1999), and the more difficult problems involve counter-intuitive moves. On these problems, the subjects must keep the final goal in mind while planning a subsidiary move away from that goal. As already mentioned, Koechlin et al. (1999) have suggested that situations of this sort specifically engage the polar PF cortex. These activations reflect an elaboration of the goal hierarchy, perhaps by adding a new level. We return to this possibility later.

Task instructions

When people perform laboratory tasks or go on errands, the experimenter first tells them what to do. This means that while the subjects carry out the tasks, they need to remember what they should do. Table 9.3 lists activations in two situations that involve maintaining tasks in memory. In the first situation, the subject must maintain the task in short-term memory. In the second, the subjects perform two tasks, and they need to maintain one of them in short- or long-term memory as they perform the other task.

Maintaining current task rules in memory

As Chapter 7 mentions, Wallis et al. (2001) taught monkeys whether the matching or nonmatching rule applied on any given trial by training them to treat a low tone as an instruction to apply the matching rule and a high tone as an instruction to apply the non-matching rule. In a related imaging experiment, Bunge et al. (2003) taught human subjects that one nonsense sound, ‘pohu’, meant match and that another nonsense sound, ‘siba’, meant nonmatch. On each trial, one of these instructions preceded a delay period and the choice items appeared after the delay. Activation occurred in the ventral PF cortex during the delay period.

Rather than presenting subjects with nonsense words, Sakai and Passingham (2003, 2006) used English words to instruct subjects about what task they should perform in two experiments. In the first experiment, the subjects saw a series of four locations and letters. Before seeing these stimuli, the subject had received an instruction to remember either the letters or their locations and to do so either in the order they appeared or in the reverse order (Sakai & Passingham 2003). In the second experiment, the subjects saw a noun after receiving an instruction to report either a semantic judgement about the word (abstract versus concrete) or a phonological judgement (two syllables versus one or three).

In both studies, the authors found activation in the rostral part of the ventral PF cortex during the delay period. In the original papers, this activity was described as being in the frontal pole, but it is more accurate to say that the activation was somewhere near the boundary with the polar PF cortex. The authors interpreted this activation as reflecting the *task set*. A task set, in this sense, refers to the rule that guides behaviour at any given time. In the first study, the task-set activation correlated better with activation in the caudal PF cortex when subjects needed to remember *locations* in the reverse order and better with activation in Broca’s area (in a different part of the left ventral PF cortex) when subjects needed to remember *letters* in the reverse order. In the second study, the task-set activation correlated better with activation in the ventral premotor cortex when

Table 9.3 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Goals	Maintaining task rules in memory	Prospective memory for task rule
	Maintaining future tasks in memory	Prospective memory for future tasks

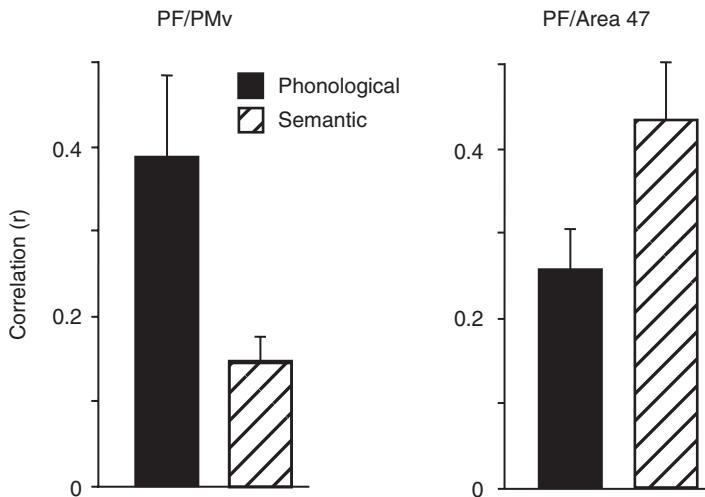


Fig. 9.4 Correlations in activation between the rostral PF cortex and a more caudal, task-specific area in two tasks, one phonological (black bars) and one semantic (hatched bars). PF/PMv: correlation between delay-period activation in the rostral PF cortex and the ventral premotor cortex. PF/area 47: correlation between delay-period activation in the rostral PF cortex and the inferior part of area 47. Error bars: SEM. Reproduced from Sakai K, Passingham RE. Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. *Journal of Neuroscience* 26:1211–18, © 2006 Society for Neuroscience, with permission.

the subjects needed to sound out the word for a *phonological* judgement and better with activation in the caudal part of the left ventral PF cortex when subjects needed to make a *semantic* judgement (Figure 9.4).

It could be argued that the delay-related activations reflect the memory of task instructions rather than the preparation to perform a specific task. But a study by Haynes et al. (2007) ruled out this interpretation. Their task did not involve any verbal instructions. Instead, at the beginning of each trial the subject decided what operation to perform, specifically whether to add or subtract numbers. A variable delay then intervened before the numbers appeared. The authors analysed the delay-period activation in various PF areas using a method that discriminated between activation patterns for different trial types. Despite the lack of a verbal instruction, a pattern analyser could detect whether the subject was going to add or subtract at the level of 60–70% correct.

If task-set activations reflect the maintenance of tasks in memory, damage to areas with such activation should lead to errors and alter activations in the task-specific areas. So Rowe et al. (2007) studied four patients with large lateral frontal lesions. The patients and control subjects saw a series of letters that appeared in any of four locations, and they had to remember either the locations or the letters (Figure 9.5). The patients with PF lesions made more errors than healthy subjects when the instruction changed from one trial to the next (shift trials). If, on the other hand, the instruction repeated from trial-to-trial, they made fewer errors than the control subjects (stay trials). Rowe et al. explained this result by suggesting that the patients failed to keep the current task in memory and by default repeated the same task as on the previous trial.

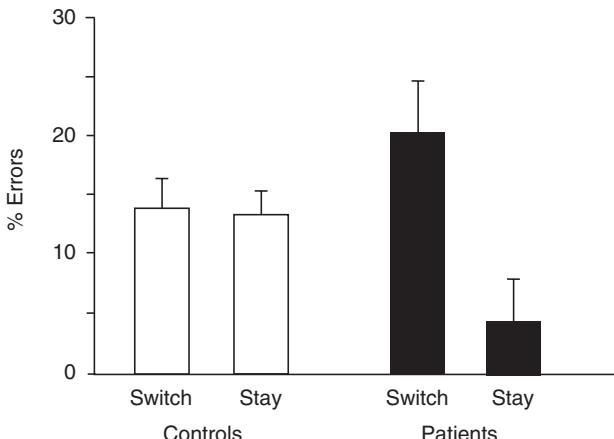


Fig. 9.5 Behavioural results on the memory and attentional selection task used by Rowe et al., for patients (black bars) and control subjects (white bars). Ordinate: percent errors in remembering the locations or letters. On stay trials, the task was the same as on the previous trial; on switch trials, the task was the opposite of that on the previous trial. Error bars: SEM.
Reproduced from Rowe JB, Sakai K, Lund TE, Ramsoy T, Christensen MS, Baare WF, Paulson OB, Passingham RE. Is the prefrontal cortex necessary for establishing cognitive sets? *Journal of Neuroscience* 27:13303–10, © 2007, Society for Neuroscience, with permission.

Rowe et al. also analysed the correlations between the delay-period activations in the caudal PF cortex and in the posterior parietal cortex, as well as between the caudal inferior frontal gyrus (Broca's area) and the temporal cortex. They found lower correlations in the patients than in control subjects (Figure 9.6). And this was true both for stay trials and shift trials. The results show that the lesion disrupted the covariance between activation in the caudal PF cortex and the task-specific regions with which it is connected.

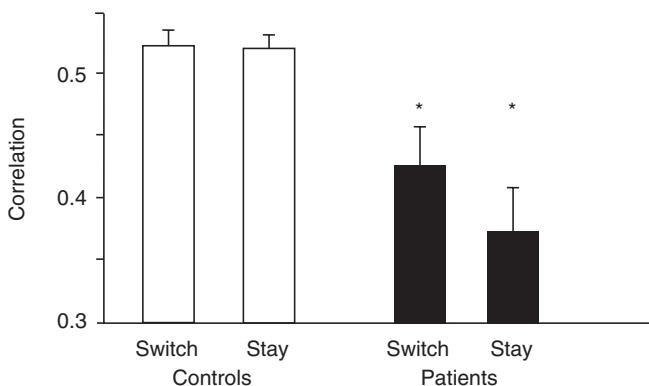


Fig. 9.6 Imaging results on the task used by Rowe et al., for patients (black bars) and control subjects (white bars). Correlations between delay-period activations in the caudal PF cortex and task-relevant areas in the parietal and temporal lobe, separately for stay and shift trials.
Reproduced from Rowe JB, Sakai K, Lund TE, Ramsoy T, Christensen MS, Baare WF, Paulson OB, Passingham RE. Is the prefrontal cortex necessary for establishing cognitive sets? *Journal of Neuroscience* 27:13303–10, © 2007 Society for Neuroscience, with permission.

These findings relate to the fundamental function of the PF cortex because they indicate that the PF cortex is involved in maintaining the current task rule in memory. Recall that the proposal in Chapter 8 refers to the idea that the granular PF cortex provides a mechanism for learning and applying abstract rules.

Maintaining future tasks in memory

In the studies just mentioned, the subject carried out one task on each trial. But subjects can also perform two tasks on each trial, and in this situation they need to maintain one in memory while performing the other. The term ‘prospection’ has been used in this restricted sense (Burgess et al. 2000). We place this usage in quotes because we use the same term in a different way (see the Glossary).

In a study that we referred to earlier, Koechlin et al. (1999) required subjects to match a series of upper-case letters, pressing the right button for a match and the left for a non-match. In the branching condition, the subjects needed to judge whether upper-case letters matched, while at the same time performing a secondary task. This second task required them to note the lower-case letter ‘t’ when the case changed. In a comparison condition, the subjects alternated between these two tasks. The polar PF cortex was more activated in the branching condition than the alternation condition, possibly because it enabled subjects to suspend their performance of the primary task while they turned their attention to a more immediate secondary task.

If the polar PF cortex (area 10) plays a special role in holding two tasks in memory at the same time, then one would expect patients with lesions of this area to be poor at doing so. In two studies, Burgess and colleagues gave a series of simple tasks to patients, with the requirement that they perform all of them (Burgess et al. 2000, 2007). The patients attempted fewer tasks and switched less often between tasks than did healthy people. The authors concluded that the patients failed to keep all the tasks in prospective memory while they attempted them. The human polar PF cortex therefore appears to support multitasking behaviour.

However, the lateral polar PF cortex does more than simply hold more than one task in memory. It also holds more than one potential goal in memory, as well. Boorman et al. (2009) scanned subjects while they made a choice among two object-like goals. They found activation in the lateral polar PF cortex that correlated with the relative advantage of the alternative choice, the potential goal not chosen. And in a follow-up study that involved several alternative choices, the lateral polar PF cortex had activation that reflected the reward value of the best of these unchosen alternatives (Boorman et al. 2011). Later, we discuss the possibility that the lateral polar PF cortex represents potential choices and evaluates the likely outcome of each one. This cognitive operation amounts to trial-and-error behaviour conducted in the imagination, and we think that this capacity makes a crucial contribution to human cognition.

Summary

In our proposal, we suggested that when a monkey cannot act immediately, the PF cortex can prospectively encode goals until the time comes to act. However, it is important to

distinguish between prospective coding of goals and retrieving them from long-term memory. Patients with large rostral PF lesions, including the polar PF cortex, can repeat the instructions if asked; but they often fail to put them into practice, for example, when carrying out a series of three simple tasks (Burgess et al. 2000). They probably can recite the instructions because, when asked about them, the patient retrieves the appropriate representation from long-term memory. Although this capacity remains intact, the same patients nevertheless have an impairment in maintaining these representations in memory, which they must do as they perform a series of tasks. We suggest that a failure to maintain goal representations in this way leads to what Duncan et al. (2008) have called goal neglect.

Monitoring intentions

The final set of activations that involve the goal hierarchy concerns the monitoring of intentions. Table 9.4 presents the two activations considered here.

Monitoring own intentions

We argue in Chapter 8 that the PF cortex generates goals attentively, which we contrast with automatic control, and we present data in this chapter showing activation in the PF cortex when human subjects attend to what they are doing (Rowe et al. 2002a). The subjects performed a sequence of finger movements, and the experimenters simply told subject to think about their actions.

Simply telling subject to attend to their action is an inelegant way of manipulating attention. So, in a later study, Lau et al. (2004b) used the task introduced by Libet and his colleagues (1983). On this task, the subjects are instructed to move a finger whenever they want. To enable the subjects to time their intention, a spot moves around a clock face, and the subjects have to note and remember the spot's location when they first became aware of their intention to act. This location corresponds to a time, and subjects typically report that the awareness of their goal occurred ~200 ms before movement onset.

Lau et al. (2004b) used this task in an imaging experiment. In one condition, the subjects had to report when they became aware of their intention to move, and in the comparison condition they simply reported when they actually moved their finger. Compared to the latter condition, reports about intention were associated with activations in the preSMA, the posterior parietal cortex, and the mid-lateral PF cortex (area 46). The earlier the subjects reported awareness, the greater was the degree of activation (Lau et al. 2006). The activation was located on the border between the preSMA and SMA, as illustrated in Figure 9.7 (point 2).

Table 9.4 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Goals	Monitoring own intentions	Attending to action
	Monitoring intentions of others	Using signs to predict the actions of others

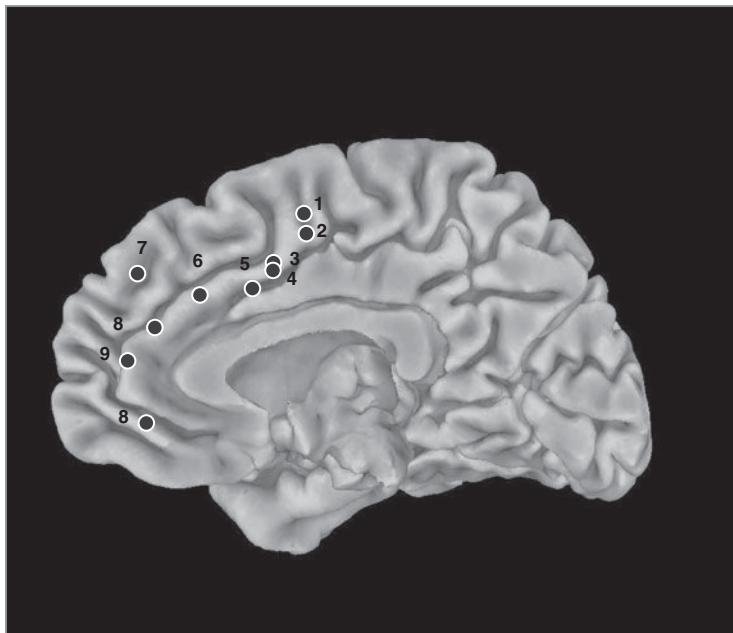


Fig. 9.7 Peak voxels for medial activations reflecting several cognitive processes: 1, attention to action; 2, attention to intention; 3, attention to hunger; 4, attention to emotion; 5, attention to heart rate; 6, reflection on trait words regarding oneself; 7 reflection on one's own performance; 8 (two peaks), retrieval of episodes in one's own life; and 9, reflection on the mental states of others. Medial view, rostral is to the left.

In a subsequent experiment, Lau et al. (2006) found activation in the caudal cingulate motor area when subjects reported when they actually moved their finger (Figure 9.7, point 1). Lau et al. analysed the covariance between the three activation sites when people report their intention and found a significant influence on the preSMA from the PF cortex but not from the posterior parietal cortex.

In these experiments, the subjects simply reported when they first became *aware* of a particular mental state. However, human subjects can make other judgements concerning their mental states. For example, in an experiment by Gusnard et al. (2001), subjects viewed a series of pictures and pressed one of two keys depending on whether the picture gave them a pleasant or unpleasant feeling. Gusnard et al. called this the introspection condition. In the comparison condition, the subjects pressed keys according to whether the scene was indoors or outdoors. More activation occurred in the dorsal paracingulate cortex and dorsomedial PF cortex (area 9) during the introspection condition, and similar results have been reported when subjects judge whether pictures make them feel aroused or alert (Goldberg et al. 2006).

In an experiment by Herwig et al. (2010), the subjects either thought about their goals or about their emotions. Activation occurred in the dorsal paracingulate cortex for goals and more posteriorly in the anterior cingulate cortex for emotions. The dorsomedial PF

cortex (area 9) became more activated when subjects made judgements about their own mental states but became less activated when subjects made judgements about stimuli (Gusnard et al. 2001; Herwig et al. 2010).

Monitoring the intentions of others

Frith (2007) has suggested that people have the ability to represent the intentions of others because they can represent their own intentions. In most of the studies in which subjects judge the mental states of others, the activations occur in the dorsal paracingulate cortex or in neighbouring parts of the medial PF cortex (Amodio & Frith 2006). Point 9 in Figure 9.7 shows the peak activation from a meta-analysis (Gilbert et al. 2007).

Imaging activations also reveal a relationship between judgements about others and about oneself. When subjects decide whether a particular trait applies to themselves, activation occurs in the dorsal paracingulate cortex (point 6 in Figure 9.7). When they decide whether these trait words apply to someone else, the peak of activation occurs in much the same place (Ochsner et al. 2005).

Reading the intentions of others has many advantages in human societies. One of the less obvious ones involves imitation. People can imitate by merely copying an observed action, but this kind of behaviour becomes much more significant when one attempts to achieve the same goals by copying some else's actions. Stout et al. (2011) scanned both novices and expert flint knappers as they observed someone making flint tools. Their experiment involved two types of tools: Oldowan choppers, made by simply striking a flint flake off a core, and Acheulian hand-axes, made by a complicated series of strikes on the edge of the core, in order to produce a continuous blade.

In both novices and experts, greater activation occurred in the ventral PF cortex when observing the manufacture of complex hand-axes versus simple choppers. However, only in experts did the activation also occur in the medial PF cortex. Stout et al. suggested that this reflected the fact that the experts could read the intentions of the tool maker better than the novices could.

Summary

Activations occur in the preSMA when people attend to their own actions, and more rostrally in the dorsal paracingulate cortex, dorsomedial PF cortex (area 9), and other parts of the medial PF cortex when they monitor their own intentions. The ability to monitor their intentions implies that people can monitor their other mental states, as well, and this ability enables them to read the mental states of others. Amodio and Frith (2006) pointed out that activations for reflection on the mental states of others typically lie rostrally in the medial PF cortex (point 9 in Figure 9.7), whereas the activations for monitoring one's own intentions and movements lie more caudally (points 2 and 1 in Figure 9.7). And we suggested earlier that one of these more rostral parts of the medial PF cortex, the dorsal paracingulate cortex, might have evolved in the human–ape lineage. In the context of the activations discussed in this section, this area might elaborate the goal hierarchy that apes and humans inherited, and thus provide a new capacity. We take up that topic again in the conclusion of this chapter.

Monitoring outcomes

We now turn to activations that involve outcome monitoring, as listed in Table 9.5.

Monitoring internal states

Relief from hunger and pain are among the many outcomes of choices and actions. Figure 9.7 shows activations in the anterior cingulate cortex when people attend to feelings of hunger (point 3) (Siep et al. 2009), to emotion-inducing stimuli (point 4) (Luo et al. 2007), or to their heart rate (point 5) (Critchley et al. 2004). The peaks for these activations tend to lie within the anterior cingulate cortex, and they probably reflect inputs about the vascular system from baroreceptors, about the stomach from mechanoreceptors, and about tissue damage from nociceptors (Vogt & Derbyshire 2009).

Monitoring outcomes

In most imaging experiments, visual or auditory cues signal outcomes, rather than providing subjects with food or compelling them to endure pain. Early studies suggested that when subjects monitor outcomes, the activations in the anterior cingulate cortex reflect detecting or monitoring errors (Carter et al. 1998). This view was later refined to suggest that these activations relate to the conflict that such negative feedback induces (Botvinick et al. 2001).

However, recent work has overturned this idea. As Chapter 3 mentions, Walton et al. (2004) devised a study that improved on earlier ones in which only errors that provided feedback. In the experiment by Walton et al., positive feedback provided as much information as a negative feedback. In this balanced condition, Walton et al. showed that anterior cingulate activation did not differ when the subjects monitored positive versus negative outcomes. Thus the anterior cingulate cortex does not function in either error or conflict detection per se, but rather in the monitoring of outcomes more generally.

Monitoring oneself

The degree to which the outcomes matter depends on a subject's understanding of the task requirements. Bengtsson et al. (2009) told one group of subjects that they had to take a memory test, the *n*-back task, and that this test measured their intelligence. They told another group of subjects that the task simply tested various task parameters, without any reference to intelligence.

In both groups, activation occurred in the anterior cingulate cortex when the subjects detected that they had made errors, and this activation was in the same location as in previous studies of error detection and monitoring (Botvinick et al. 2004). However, in the group that thought they were taking an intelligence test, the dorsal paracingulate

Table 9.5 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Outcomes	Monitoring internal states	Evaluating outcomes
	Monitoring outcomes	Evaluating outcomes
	Monitor oneself	Re-representing outcomes of own behaviour

cortex also became activated, and it did so both when subjects monitored the outcome and when they rated their own performance. This finding suggests that the activations occurred when the subjects judged their own performance.

We have already mentioned that people can establish a neural representation of themselves. Point 6 in Figure 9.7 shows the peak of activation when subjects decide whether trait words apply to themselves (Ochsner et al. 2005). This peak lies near the peak for the activation when subjects reflect on their own performance (point 7).

Summary

Figure 9.7 illustrates the caudal-to-rostral organization of activations within the medial PF cortex. One can classify these activations into several groups: actions and intentions (points 1 and 2), internal states (points 3, 4, and 5), and rating or monitoring of oneself (points 6 and 7). A more rostral point (9) has activations for reflection on the mental states of others.

Chapter 8 explains the goal hierarchy of the PF cortex and how it seems to extend the functions of the more caudally situated premotor areas. In a nutshell, we suggest that the prefrontal levels of this hierarchy extend an action hierarchy into a goal hierarchy. This idea has an important implication for the outcome hierarchy, as well. On this view, rostral activations reflect an elaboration of a more caudally situated system that monitors the outcomes of actions. People can monitor not only their own actions but also their own mental states, including their intentions. This process involves meta-cognition: knowledge about one's own knowledge. Lau and Rosenthal (2011) suggested that meta-cognition, in turn, depends on re-representation: the representation of other representations. As we noted earlier, when subjects rate their own performance or describe their self-image, the activation peaks lie in the dorsal paracingulate cortex. And as the first part of this chapter suggests, a dorsal paracingulate cortex might have evolved in apes or humans. It is as if a further level has been added to the hierarchical processing, thus elaborating it.

Associative learning

So far, we have attempted to relate activations that occur in the human PF cortex to the context, goal, and outcome hierarchies that Chapter 8 describes. They either reflect these hierarchies in more-or-less the same way as in monkeys or they exemplify relatively straightforward elaborations of these hierarchies. The following sections consider the relationship of these hierarchies to each other and to events, rules, and memories. We begin with elaborations of the mappings between goals and contexts (Table 9.6).

Table 9.6 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Mapping goals to contexts	Verbal paired associates	Mapping cue word to response word
	Word meanings	Arbitrarily mapping word to a referent
	Semantic knowledge	Associating representations, categorizing

Verbal paired associates

In many of the imaging experiments discussed so far, the subjects learned by trial and error. But people can learn a different way, as well. The experimenter can simply present information, such as pairings between items, and later test the subjects.

Verbal paired associate learning provides one example of this approach. The subjects hear a series of word pairs such as ‘cabbage–pen’, and then respond to the cue ‘cabbage’ by saying ‘pen’. Activation occurs in the ventral PF cortex during the initial presentation of verbal paired associates (Fletcher et al. 1995), and it significantly increases when the subjects have already learned a set of associations, but the associations change. Dolan and Fletcher (1997) first taught subjects the associations between pairs such as ‘dog–boxer’. During some of the scans, the original associations changed, such as ‘dog–labrador’ or ‘sportsman–boxer’. During other scans, the subjects learned new associations, such as ‘food–biscuit’. The ventral PF cortex showed greater activation for the altered mappings than for the new ones. In agreement with these neuroimaging results, frontal lesions cause impairments on learning a set of paired associates (Dimitrov et al. 1999).

The proposed function of the PF cortex accounts for these results without much difficulty. The impairments in patients result from an inability to retrieve a goal representation, such as a word or a picture, based on a context. The activations reflect this process in healthy subjects. People can perform this task by accessing their memory of the original presentation of the items. Because the items only appeared once, the task can be said to rely on a single event, and so the term episodic memory has been used for performance on tasks of this sort (Fletcher & Henson 2001). On this view, the PF cortex activation reflects the generation of the goal item on the basis of memory of a single event, as Chapter 8 emphasizes.

Word meanings

Both Murray et al. (2002) and Passingham (2008) have suggested conditional tasks as a model for learning the meaning of words. They share an arbitrary relationship between two representations. And activations occur in the PF cortex as subjects learn to associate words with their referents. Klingberg and Roland (1998) presented subjects with a series of meaningless sounds, each one paired with an abstract picture. The activation during the presentation of the cues lay caudally near the border between the ventral and dorsal PF cortex.

Tsukiura et al. (2002) studied associations between names and faces. In their experiment, each face had previously appeared together with a name in text. During retrieval of these associations, activation for relatively unfamiliar faces and names occurred bilaterally near the border of the dorsal and ventral PF cortex. Some of the face–name pairs had, however, become very familiar to the subject through several prior presentations. For familiar faces and names, the activation occurred in the caudal part of the superior temporal sulcus. This finding suggests that although the PF cortex participates in the initial learning and retrieval of the associations, the temporal lobe ultimately stores the linkage.

Although the *mechanism* for learning word meanings may parallel that for learning paired associates in monkeys, people *use* these associations in a fundamentally different way. A person says ‘book’ in order to cause the listener to retrieve a representation of a book from his or her memory. In this way, speakers use words to influence the mental states of others, or at least they attempt to do so. Indeed, Frith (2007) has argued that language presupposes the ability to read the mental states of others. The desired mental state of the listener thus corresponds to the goal of the speaker and the spoken word corresponds to the action that achieves the goal. Because of this relationship, the proposed function of the PF cortex, as Chapter 8 propounds, can account for speech-related activations in the human PF cortex: the speaker generates a goal, which has something to do with the mental state of the intended recipient, and the goal leads to the appropriate action through the medium of speech.

The fundamental function of the PF cortex relates to word learning in another way, as well, which concerns the speed of learning. As with the learning of face-to-name mappings, humans can learn associations between sounds and their referents in one presentation. Infants learn these associations very rapidly indeed through a process called fast mapping (Bloom 2000). The evidence that Chapters 7 and 8 review shows that the granular PF cortex contributes to something like fast mapping in monkeys; so activations in homologous areas during word learning should come as no surprise.

Semantic or associative knowledge

The learning of word meanings involves what Tulving (1983) has called semantic memory, which he contrasts with episodic memory. Episodic memory refers to memory for past events in one’s life, often called autobiographical memory, whereas semantic memory refers to knowledge about objects and other facts about the world. People know, for example, that pyramids and palm trees occur naturally in Egypt but fir trees do not. The pyramid and palm trees task tests this kind of knowledge (Howard & Patterson 1992).

Vandenbergh et al. (1996) devised a difficult version of this task, which Chapter 1 mentions. As an example of one trial on this test, the subjects saw a picture of a pair of pliers and had to choose either a saw or a wrench. Because a wrench and pliers can both grip things, subjects should use this fact about the world to choose the wrench. For either the pictorial or verbal form of the task, activation occurred in the left ventral PF cortex, as well as in the left middle and inferior temporal cortex. Phillips et al. (2002) presented pictures of objects and required the subjects to judge what could be done with them. The PF activation resembled that observed by Vandenbergh et al. Thus the use of factual knowledge leads to activation of the ventral PF cortex.

To find out whether activation in the ventral PF cortex is necessary for correct performance, Price et al. (1999) studied a patient with a left ventral PF lesion on an easier version of this test. Surprisingly, the patient did well on the task. The patients who do badly have lesions of the rostral temporal lobe, near the rhinal sulcus (Davies et al. 2004). This finding suggests that the temporal lobe stores semantic memories, and not the PF cortex.

However, this conclusion does not mean that the PF cortex plays no role in semantic memory. It could be that the patient with a PF lesion performed normally because time had elapsed since the lesion, and this could have allowed some recovery of function. If so, then temporarily inactivating the left ventral PF cortex should have an effect on this task. So Whitney et al. (2010) applied rTMS to this area as they presented subjects with a word. The subjects needed to choose from a set of three words the one that had a closely associated meaning. The task came in an easy version and a difficult one. In the easy version, for example, 'salt' mapped to 'pepper' rather than to 'machine' or 'land'. In the difficult version, 'salt' mapped to 'grain' rather than to 'radio' or 'adult'. Disruptive stimulation over the caudal part of the left ventral PF cortex caused a significant increase in errors in the difficult condition. In a similar experiment, Gough et al. (2005) also showed that the effect was selective in that it did not cause errors when subjects had to judge whether two words rhymed.

These results indicate that the ventral PF cortex plays some role in the retrieval of semantic memories, especially for difficult tasks. However, the exact contribution remains uncertain. Fletcher and Henson (2001) have reviewed various proposals, which agree only in suggesting that the PF cortex contributes in some way to the attentive retrieval of semantic memories.

We relate these findings to the fundamental function of the PF cortex by noting that these tests of semantic knowledge involve categorization. Both palm trees and pyramids belong in the category 'Egyptian'. In Chapter 7, we review the evidence that cells in the ventral PF cortex of monkeys encode categories of objects, which can sometimes depend on perceptual similarity but which sometimes do not. Cells in the ventral PF cortex of monkeys encode categories of both types. In the latter case, the association between items in a category is arbitrary and therefore must be learned. No amount of stimulus generalization will create the representation of an arbitrary category, as it could when a category depends on the resemblance of sensory features. A person has to learn that palm trees are associated with pyramids because they occur in Egypt, even though dense conical fir trees look more like pyramids than palm trees do. For these kinds of categories, the proposed function accounts for PF cortex activations because these learned associations involve the mapping of context to goals. For example, given the context of a pyramid, the PF cortex can generate a representation of a palm tree as a goal.

Unlike other animals, humans can learn facts through instruction as well as through trial-and-error behaviour. A person can learn that a pyramid goes with a palm tree even if they have never travelled to Egypt to see the associations first hand. So Maguire and Frith (2004) scanned human subjects while they learned about such facts. In one condition, the subjects read sentences that instructed them about well-known facts, such as 'a grouper is a type of fish'. In the other condition, the sentences taught them unfamiliar facts, such as 'the spy was caught as he tried to escape'. Maguire and Frith observed activations in the hippocampus during the encoding of both familiar and unfamiliar facts, especially when the subjects subsequently remembered them correctly. But they also found activations in the left ventral PF cortex, which were greater when the subjects

learned unfamiliar facts. The mediodorsal nucleus of the thalamus (MD) and left middle temporal gyrus also became activated in this condition.

Summary

We argue in Chapter 8 that because the PF cortex lies at the top of the context, goal, and outcome hierarchies it can map contexts to goals in a way that other parts of the cortex cannot. By using a single event, the PF cortex can mediate fast learning and other means of reducing errors. People can learn to map cues words to response words in one trial, and they can learn to map words to their referents after hearing the association once (Bloom 2000). Unlike other animals, people can learn new facts without making any errors at all, in part because they can learn from instructions. In the concluding section, we explain the significance of this ability. Learning systems that depend on *physical* trial-and-error behaviour cannot avoid errors, but those that engage in *mental* trial-and-error or make choices based on instruction can, in principle, avoid errors entirely.

Episodic memory

When discussing event memory in Chapter 8, we took care to say that we do not know whether, when nonhuman animals retrieve the memory of events, they have any awareness of those memories, a concept sometimes equated with the term *recollection*. Thus, we deliberately avoid using the term episodic memory as introduced by Tulving (1983). Tulving, among others, have specified that to qualify as a genuine episodic memory, people must be aware of the content of that memory and they have some sense of re-experiencing or recollecting the event.

Table 9.7 lists activations that relate to the retrieval of episodic memories.

Retrieval of events

People can be asked to remember single events in their life, such as buying a ticket at a particular cinema booth at a particular time. When subjects retrieve these memories, activations occur in medial PF areas such as medial area 9, as well as in the retrosplenial and hippocampal cortex (Hassabis et al. 2007b; Summerfield et al. 2009). The two points labelled 8 in Figure 9.7 illustrate the activation peaks in the medial PF cortex. When considered along with the other points in the figure, one can appreciate a hierarchy in which the more rostral sites involve the memory of autobiographical events, occurrences that

Table 9.7 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Generating goals from events	Retrieving events from memory	Retrieving episodic memories
	Imagining future events	Generating events from episodic memory
	Source memory	Generating the context from associated items

involved the subjects themselves. From caudal to rostral, the hierarchy involves actions, attention to actions, attention to intentions, and attention to other aspects of one's self and one's performance.

These activations thus agree with our proposal, which says that the PF cortex can generates goals based on single events. An autobiographical memory represents the quintessential one-time event. It is not, however, clear whether the activation in medial area 9 is critical for retrieving the memory. Thais and Petrides (2008) studied patients with frontal lobectomies, and of the 11 patients, six had lesions that included the medial PF surface, including the areas activated during the recall of events. Yet the patients recalled as many memories of past events in their life as did the control subjects, albeit with some disorganization.

But the lesions were unilateral, and so the results are not conclusive. Bilateral lesions lead to firmer predictions, and Bird et al. (2004) have described a patient with a very large bilateral medial frontal lesion. It included medial areas 9 and 10, as well as the dorsal and ventral paracingulate cortex. The patient could recall *facts* about themselves and their life, but had a very poor memory for autobiographical *events*. However, there was also damage to the fornix, and this could be responsible for the impairment in memory.

So further work is needed on this topic. In particular, we need to find out whether the medial PF cortex plays a necessary role in retrieving episodic memories or for generating goals on the basis of such memories. Our proposal relates to the generation of a goal rather than the retrieval of a memory *per se*.

Imagination of future events

People can not only retrieve their memories of past events, but they can also imagine events in the future, commonly known as scenarios. And some evidence indicates that the mechanisms allowing them to do so are related to episodic memory (Addis et al. 2007). First, when subjects imagine future events, the peaks of activation overlap to a great extent with those for retrieval of past events (Hassabis et al. 2007a). Second, when patients with amnesia for past autobiographical events try to imagine future ones, they are very poor at doing so (Hassabis et al. 2007b).

In imagining experiments, people have been asked to put together aspects of their own past experience (Schacter et al. 2007). Summerfield et al. (2010) asked subjects to use their imagination to construct scenes. For example, they asked subjects to imagine putting together a 'wooden bench', a 'plain beige carpet', a small cabinet', and 'a pair of woolly gloves'. When the subjects imagined the first item, an object, activation occurred in the mid-lateral and ventral PF cortex. When the subjects combined three elements in their imagination, to construct an imaginary scene, activation occurred in the ventral PF cortex and in the polar PF cortex, along with the retrosplenial and hippocampal cortex.

Given the ability to spin out scenarios in the imagination, people can prepare for alternative courses of events in order to achieve desired outcomes. Tulving (2005) called this cognitive function *mental time travel*, and he applied the term both to travelling into the past via event memory and to travelling into the future via the imagination.

Scenarios and mental simulations play a crucial role in human cognition. As a consequence, people can play out possible behaviours in their imagination. To use a phrase that we have used earlier, they can engage in imaginary (mental) trial-and-error behaviour. Thus people can consider particular courses of action, think through the potential consequences, and switch to an alternative course of action when the imagined consequences do not meet their needs. Boorman et al. (2009) showed that when subjects make one choice, activation in the polar PF cortex tracks the relative advantage of switching to an alternative choice.

Summerfield and Koechlin (2009) have specifically suggested that the most rostral parts of the human PF cortex process event information that involves a distant time, and Krueger et al. (2007) have made a related suggestion involving the rarity of events. The first part of this chapter suggests that the lateral polar PF cortex might have evolved in humans or the ape–human lineage and, if this is the case, then goal generation over increasingly distant time frames and less frequent events could represent a new capacity mediated by a new PF area in this lineage.

Source memory

Episodic memories are embedded in the spatial and temporal context in which an event occurred. This property has led to specific tests of *source* memory, as opposed to *content* memory. In these tests, the experimenter presents an item and the subject needs to specify the context in which that item had appeared.

For example, Kostopoulos and Petrides (2008) presented the words ‘advice’, ‘danger’, ‘review’, and ‘status’ on differently coloured backgrounds. At the retrieval stage, subjects had to report whether a particular word and colour had appeared together. A control condition simply tested whether the subjects remembered the word. The former condition led to more activation in the left ventral PF cortex.

In a related experiment by Henson et al. (1999a), subjects read two different lists of objects or words and later reported the list in which a probe item appeared. They also presented items above or below a line, and asked for their original location. Activation occurred in the right ventral PF cortex when they assessed source memory in either way, both of which require the retrieval of contexts based on event memories.

King et al. (2005) went on to devise two versions of the source memory task, one with high interference and the other with low interference. The subjects navigated their way through a virtual reality environment on a screen and saw objects being presented by different people in that environment. In the high interference condition, the same people presented several objects; in the low interference condition, each person presented only one object. The high-interference condition led to greater activation in the ventral PF cortex.

Activations during source memory tasks reflect the fundamental function of the PF cortex in a straightforward way, but one that is slightly different from any discussed to this point. Chapters 7 and 8 explain that the PF cortex generates a goal when cued by a context. A source memory task has the opposite requirement. The goal item cues the

retrieval of the context in which it had appeared. These tasks thus draw on event memory and the mapping of goal to context.

Summary

We follow Tulving and others in believing that the human ability to imagine events in the distant future is related to the ability to retrieve the memories of past events. However, in spite of the fact that people can think far into the future, the fundamental role of the PF cortex remains much as it was in our distant anthropoid ancestors. Chapter 8 proposes that the primate PF cortex generates goals based on a current context. When people imagine future events and scenarios, the generation of imagined goals depends on imagined contexts. This is what we mean by an elaboration.

Thus far in this section, and in this book generally, we have skirted around the issue of conscious awareness. We have mentioned that recollection implies such awareness, but little more. But no discussion of the human brain, and especially the human PF cortex, would be complete without dealing with the concept of consciousness to some extent. It has given rise, for example, to a distinction between *recollecting* an event and *knowing* that it occurred (Henson et al. 1999b). There is, as yet, no agreement as to the relation between this distinction and the degree of confidence that a person has in their memory (Kim & Cabeza 2009).

However, no one challenges the belief that people can be aware of their memories, just as they can be aware of stimuli and their intentions. One idea about how this comes about involves the concept of re-representation. According to this view, a judgement about recollection is a meta-cognitive judgement, and it would not be surprising if meta-cognition involves a new level of hierarchical processing, one that re-represents the information and processes of lower levels.

Reasoning

Up to this point in this chapter, we believe that our proposal accounts for the imaging activations reasonably easily. We have suggested some modest elaborations of the function that Chapter 8 proposes, and we have introduced the concept of 're-representation' to account for meta-cognition. The latter point has some major implications, which we take up in the concluding section, but we feel as though we stand on firm ground. However, in the next two sections, which discuss activations that relate to reasoning (Table 9.8) and moral or social cognition (Table 9.9), we recognize that the ground is much less solid. In both cases, we appeal to the notion of abstract rules. In doing so, we are well aware of the danger that comes from using a formulation so vague that it can explain anything. Nevertheless, we explore how the fundamental function that we

Table 9.8 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Abstract rules	Reasoning	Learning rules and applying to new problems

propose for the primate PF cortex could have developed into one that could support analogical and metaphorical reasoning, as well as the moral, social, and legal rules that bind human societies. We do so without pretending to provide a complete solution to any of these problems.

Much research on human reasoning has used the ‘Raven’s progressive matrices’ task (Raven et al. 2003). Devised as a nonverbal intelligence test, many cognitive psychologists have taken it to be a good measure of fluid reasoning (Cattell et al. 1973) or general intelligence, sometimes called g (Duncan 2010a). We accept that the concept of general intelligence remains controversial among the proponents of evolutionary psychology, and they have made some compelling arguments in favour of more specialized problem-solving systems. Yet Plomin and Spinath (2002) have shown that g accounts for nearly all the genetic variance on a variety of psychometric tests of general intelligence, and this shows that the variance that is in common amongst these tests relates to something that is heritable.

Figure 9.8 shows a simple item from the Raven’s task. The subjects examine the first row of the matrix and have to develop a hypothesis about what transformation occurs to produce the second item. They then inspect the first item in the test line, on the bottom row of the matrix, and have to choose the missing item from the four stimuli that appear below the matrix. The subject might be tempted to supply the large black square, but the correct choice is the large black circle.

On more difficult problems of this task, experimenters present three lines, with three items per line. The subject has to develop a hypothesis about the rule obeyed on the first two lines in order to supply the missing item on the third line.

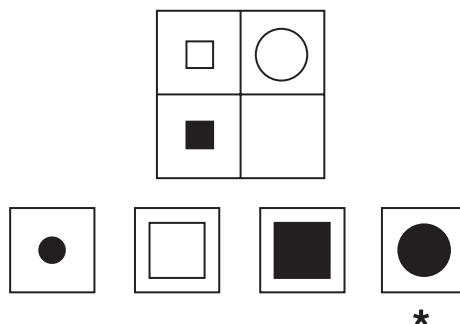


Fig. 9.8 Example of a problem presented to subjects in the Raven’s progressive matrices test. The subject must choose one of the four items at the bottom and place it in the missing space in bottom right cell of the matrix. From left to right the shape changes to a circle but the fill remains the same (white). Accordingly, as marked by the asterisk, the correct solution is the object that reflects the same change in shape (square to circle) while maintaining a constant fill (black). Reproduced from Duncan J. *How Intelligence Happens*. © 2010, Yale University Press, with permission.

Of course, a person taking the Raven's test could use words to describe the transformation or relation. But Levine et al. (1982) have described a patient who became aphasic after a stroke and was said to have lost all 'inner speech' in the sense of 'hearing' oneself thinking. Yet he could solve Raven's problems as well as expected for someone of his age and occupation. So it seems to be a genuinely nonverbal task.

When people perform the Raven's task, the mid-lateral and ventral PF cortex becomes activated (Prabhakaran et al. 1997). And Christoff et al. (2001) claimed that for more difficult problems the activation extends more rostrally, to near the border of the polar PF cortex. We explain earlier in this chapter that this lateral part of the polar PF cortex might have evolved in the ape–human lineage.

Duncan et al. (2000) used Cattell's culture-fair test (Cattell et al. 1973), which resembles the Raven's progressive matrices task. They also found activation in the mid-lateral PF cortex, and they also found that both spatial and verbal problems led to similar activations. Patients with either prefrontal or posterior parietal lesions have impairments on these tests, but those with temporal lobe lesions do not (Woolgar et al. 2010).

All of these problems require subjects to make judgements about relations, and analogies also test the understanding of relations. Bunge et al. (2005) asked subjects to say whether 'chain-link' was analogous to 'bouquet-flower'. When subjects made these judgements, activation occurred in the PF cortex, with the peak lying near the border with the polar PF cortex.

A subsequent study (Wendelken et al. 2008) used explicit analogies such as 'shoe is to foot as glove is to hand'. In one condition, the subjects evaluated whether the relations were analogous, and this condition encouraged the subjects to directly compare the two relational components: shoe–foot and glove–hand. In this condition, activation occurred near the border between the lateral part of the polar PF cortex and the mid-lateral PF cortex (area 46). In another condition, the subjects were presented with 'shoe is to foot as glove is to ?' and needed to supply 'hand'. This condition taxed semantic retrieval, and in this condition activation occurred in the ventral PF cortex.

We suggest two ways in which our proposal might account for these activations. First, the solution to each problem or analogy requires the generation of a goal on the basis of a context. On the Raven's task, the first one or two lines provide the context. Second, the analysis of that context requires the recognition of abstract rules. On the more difficult problems, the items in the first and second line differ from each other, but they obey the same abstract rule or relation. The person then has to solve the problem by applying that abstract rule to the items on the third line. The analogy task also involves abstract relational rules. Chapters 3–8 argue repeatedly that the primate PF cortex plays a necessary role in guiding behaviour by abstract rules.

Although we argue that the capacity for analogical and metaphorical reasoning can be viewed as an elaboration of hierarchies and that it requires the application of abstract rules, we recognize the need to be more precise. As we said earlier, we understand the danger of vague formulations that can explain anything. So in the concluding section, we suggest that the elaboration of the fundamental function advanced in Chapter 8 occurs

via a specific mechanism: re-representation. On this view, when subjects judge whether ‘bouquet–flower’ is analogous to ‘chain–link’, they have to compare two apparently dissimilar relations, and to do so they have to form a representation of the relation between two relations, one for each word pair.

Summary

We suggest that the fundamental function of the PF cortex, as advanced in Chapter 8, can be elaborated to account for reasoning. Reasoning involves the generation of a goal that is appropriate to a complex context according to an abstract rule. Later, we consider reasoning in the context of re-representation and the addition of new hierarchical levels to the human PF cortex.

Moral and social rules

We consider finally a different set of abstract rules, that is those that apply to moral and social behaviour. Rather than listing all the separate activations, Table 9.9 treats them all as an example of knowing or implementing abstract rules. Moral and social rules are abstract because they apply across different types of behaviour. Moral or ethical rules say what one ought or ought not do. Social rules govern what behaviour is appropriate in a given context.

Moral education teaches people to regulate their own behaviour by criticizing themselves when they violate moral rules (Bandura 1997). So, Berthoz et al. (2006) scanned adults while they considered different situations. In one set of conditions, subjects considered situations in which they deliberately violated social norms, for example by spitting out the food during a communal meal. In the other conditions, they considered situations involving accidental violation of norms, such as when choking on food led to spitting it out. Contrasting these conditions, Berthoz et al. found activation in medial area 32, rostral to the genu of the corpus callosum at approximately the same dorsoventral level. They also found activation as in the part of the amygdala that has connections with that part of cortex (Beckmann et al. 2009).

Moral rules regulate social life, as do social rules that regulate exchange and cooperation. Humans have a notion of fair and unfair exchanges, and the ultimatum game probes assessments of fairness. On this task, one person makes an offer and another person can either reject or accept that offer, but only in its entirety. In imaging experiments that have used this task, activations occurred in the mid-lateral PF cortex, dorsal paracingulate cortex, and anterior insular cortex when subjects responded to unfair offers (Sanfey et al.

Table 9.9 Activations in the human brain

Elaboration	Activation	Relation to fundamental function
Abstract rules	Representing moral and social rules	Learning rules appropriate for social contexts

2003). The activation in the insular cortex activation was associated with the rejection of an unfair offer, whereas the activation in the mid-lateral PF cortex was not.

To find out whether activation in the PF cortex is critical when performing this task, Knoch et al. (2006) applied rTMS to subjects for 15 minutes before getting them to play the ultimatum game. After disruptive stimulation of the right mid-lateral PF cortex, subjects increased their acceptance of unfair offers. On the other hand, they still judged the offers to be unfair.

This pattern of behaviour resembles that reported after large bilateral PF cortex lesions. As mentioned earlier, patients with large bilateral frontal lesions sometimes fail to follow instructions even though they can accurately repeat them. Duncan et al. (2008) called this phenomenon goal neglect. We attributed goal neglect to an intact ability in retrieving the rule from long-term memory and an impairment in holding the rule in short-term memory during its application.

A phenomenon similar to goal neglect occurs in patients with lesions in the ventromedial and polar PF cortex. Krajbich et al. (2009) studied patients with lesions of the ventromedial and polar PF cortex as they played the ultimatum game. The patients offered less and felt less guilty. Yet, when asked what other people would do, they knew the appropriate behaviour. That is, they knew the social norms although they failed to abide by them.

A particularly striking case comes from a patient, called EVR, who underwent surgery for a brain tumour. The patient has a very large bilateral lesion that includes ventral, orbital, and polar PF cortex, which is sometimes referred to as a ‘ventromedial frontal cortex’ lesion. Note that elsewhere in this book, we do not use the term ventromedial PF cortex in this imprecise way. Saver and Damasio (1991) tested EVR’s knowledge of social norms, and he appeared to know most such rules. Yet in his everyday life he fails to meet his social responsibilities (Eslinger & Damasio 1985). However, EVR learned about these rules and responsibilities as a child. Anderson et al. (1999) described two patients who had early damage to the PF cortex, and as adults these patients were poor on the sorts of tests used by Saver and Damasio (1991) for knowledge of social rules.

As an overall explanation for these lesion results and the results of imaging experiments, Forbes and Grafman (2010) proposed that the PF cortex mediates the knowledge of social events. Such knowledge can be tested by presenting subjects with social scripts, where the subject has to describe a sequence of social events or make judgements about such a sequence. Krueger et al. (2009) suggest that the medial PF cortex plays a particularly critical role in such judgements. Activation occurs in the medial PF cortex when subjects describe social activities, detect the correct order of social events, or detect inconsistencies.

Summary

The activations and associated lesion effects suggest that the PF cortex contributes to moral and social judgements. When people make judgements on such matters, they concern themselves with the choices that are appropriate or permissible in a social context, either for themselves or for others. One might argue that choices of this kind reflect

the proposed function in a relatively straightforward way. In social cognition, a person has to generate a goal that is appropriate to the present situation in accordance with abstract rules, which will produce a desired outcome.

This book does not deal extensively with social behaviour. Except for occasional references to group size or intragroup competition in monkeys (Chapter 2), we instead emphasize the role of the PF cortex in foraging choices. In doing so, we follow the evidence as we know it, and not very much of the evidence from lesions, cell activity, or imaging in monkeys involves social interactions. And as a result, most of our discussion of activations in the human PF cortex follows the same line. We do not mean to imply, however, that the function of the PF cortex is confined to foraging choices. Social choices involve mechanisms similar to those for foraging choices, such as identifying the context, generating appropriate goals, and maintaining those goals in memory. We recognize, however, that these concepts do not account for all that is important in social behaviour. As the social system of humans evolved, it took on complexities that imaging experiments have yet to explore.

During their evolution, early humans adapted by cooperating with each other, as they did in hunting large animals, for example (Stringer 2011). Their survival depended on group living, and groups engaged in trade and exchange, among less positive interactions (Ridley 2010). Human societies also involve intense competition, both within and between groups. Moral and social behaviour is more complex than anything yet studied in imaging experiments, and so we do not claim that concepts such as context, goal generation, and maintaining goals in memory delve very deeply into the matter.

Conclusions

This chapter explores whether the proposal that Chapter 8 sets forth can account for imaging activations in complex cognitive tasks, and it considers how the fundamental function of the PF cortex might be elaborated in the human brain.

The anatomical review in the first part of the chapter suggests the existence of new features of the human PF cortex, in comparison with the last common ancestor of humans with either monkeys or chimpanzees. We review evidence that the granular PF cortex expanded and changed shape during hominid evolution. This development had several consequences.

1. When the PF cortex increased as a proportion of the neocortex, more cortex became available for representing and re-representing information.
2. The size of the PF cortex and the dendritic spine density of its cells influenced the degree to which information could be integrated by its cells.
3. An increase in white matter volume, which contains the fibres that connect one PF area to another, allows a greater degree of cross-domain mapping.

We also presented suggestive evidence that new areas appeared along with the expansion of existing areas. If so, then these new areas might add further levels to the context, goal, and outcome hierarchies that Chapter 8 describes. This development can be seen as a continuation of a process that added the first granular areas to the brain of early

Table 9.10 Activations in the human brain

Elaboration		Activation	Relation to fundamental function
Context	C1	Sensory decisions	Identifying the context
	C2	Sensory imagery	Generating a sensory context
	C3	Sensory awareness	Re-representing a sensory context
Goals	G1	Verb generation	Generating goal items according to context
	G2	Imagine actions	Generating goals appropriate to the context
	G3	Planning	Generating sequence of goals
	G4	Maintaining task rules in memory	Prospective memory for task rules
	G5	Maintaining future tasks in memory	Prospective memory for future tasks
	G6	Monitoring own intentions	Attending to action
	G7	Monitoring intentions of others	Using signs to predict the actions of others
Outcomes	O1	Monitoring internal states	Evaluating outcomes
	O2	Monitoring outcomes	Evaluating outcomes
	O3	Monitor oneself	Re-representing outcomes of own behaviour
Mapping goals to contexts	M1	Verbal paired associates	Mapping cue word to response word
	M2	Word meanings	Arbitrarily mapping word to a referent
	M3	Semantic knowledge	Associating representations, categorizing
Generating goals from events	E1	Retrieving events from memory	Retrieving episodic memories
	E2	Imagining future events	Generating events from episodic memory
	E3	Source memory	Generating the context from associated item
Abstract rules	R1	Reasoning	Learning rules and applying to new problems
	R2	Representing moral and social rules	Learning rules appropriate for social contexts

primates and additional granular PF areas during the evolution of anthropoids (Chapter 2). We used the word elaborations for these changes, which have the potential consequence that new, higher levels could re-represent the information that lower levels represent. Chapter 8 explains how hierarchical processing could lead to the abstraction of features, and we imagine that re-representation entails a considerable degree of abstraction.

The second part of this chapter explains how the proposal that Chapter 8 advances could account for the imaging activations that occur as people perform complex

cognitive tasks. For the convenience of readers, we compile the tables that have appeared to this point in this chapter, Tables 9.1–9.9, into Table 9.10.

We have necessarily included only a sample of thousands of reported activations, but we take these to be representative of those that have been influential among cognitive psychologists. Table 9.10 assigns these activations a letter and number for future reference.

First, for the convenience of readers, we restate the proposal from Chapter 8, in its elaborated form:

The fundamental function of the granular PF cortex, as a whole, is to generate the goals—objects and places that serve as targets of action—that are appropriate given the current context and desired outcome, as evaluated in terms of current biological needs. In contrast to phylogenetically older learning systems, it can do so attentively, on the basis of a single event. As a consequence, it provides a mechanism for reducing errors, and it does so in two ways: by fast learning and by providing a mechanism for learning and applying abstract rules and strategies. When necessary, the PF cortex maintains goals and sequences of goals in prospective memory until an attempt can be made to achieve them.

Earlier in this chapter, we suggest how this proposal can account for many of the activations that Table 9.10 lists.

1. The granular PF cortex generates goals and sequences of goals. Activations occur in the granular PF cortex when people generate words (G1), imagine objects (C2), imagine actions (G2), or imaging future actions (plans) (G3).
2. The granular PF cortex generates goals attentively, not automatically. Activations occur in the granular PF cortex when people attend to their own intentions (G6).
3. The goals are appropriate to the current context. Activations occur in the granular PF cortex when people represent a context (C1), when they map response words to cue words (M1), when they map words to their referents (M2), and when they map objects to places, and vice versa (M3). In mappings, the context serves the antecedent and the target serves as the consequent, such that the context maps to the target.
4. The goals are appropriate for the desired outcome and current needs. Activations occur in the granular PF cortex when people attend to their biological needs (O1) and monitor outcomes (O2).
5. The PF cortex can generate the goal on the basis of a single event. Activations occur in the granular PF cortex when people retrieve episodic memories (E1) or retrieve the context that was associated with an event in episodic memory (E3).
6. The PF cortex can maintain the goals in prospective memory. Activations occur in the granular PF cortex when people maintain current (G4) or future (G5) goals in memory.

We believe that the activations just listed follow in a relatively straightforward way from our proposal. However, other activations in the granular PF cortex deserve more comment. These activations relate to sensory awareness (C3), reading the mental states of others (G7), monitoring oneself (O3), reasoning (R1), representing or implementing moral and social rules (R2), and imagining future events (scenarios) (E2).

It is not surprising that our proposal would not account directly for these aspects of human cognition. The proposal that Chapter 8 advances depends on ideas about anthropoid evolution and the functions of the PF cortex in modern monkeys. Understanding awareness, theory of mind, evaluation of self, analogical and metaphorical reasoning, moral behaviour, and imaginary scenarios depends on research on humans. We have already mentioned that to account for activations that relate to these concepts, we appeal to the concept of re-representation. However, we acknowledge the danger that we could invoke this concept so loosely that we could explain anything. So, in order to constrain our account, we require that an account of re-representation be tied to the specific locations of the activations that we describe, and that it be tied to the organization of the PF cortex as a whole.

Re-representation

To illustrate our method, we start by considering the activation for sensory awareness (C3). Lau and Rosenthal (2011) discuss empirical studies of awareness, and specifically compare higher-order with lower-order views of the subject. In coming down in favour of higher-order views, they suggest that perceptual awareness involves representations of lower-order sensory representations. As Chapter 7 reviews, we know that sensory information concerning objects arrives in the mid-lateral and ventral PF cortex, and we know that activations occur in these areas when subjects decide whether the stimulus is a house or a face (Heekeren et al. 2004). So we would expect re-representations of these sensory representations to occur in these areas. And indeed, in the study by Lau and Passingham (2006), an activation occurred in the mid-lateral PF cortex that related to the subject's report of whether they had seen a shape or not. This activation involves a representation of 'seeing'.

The location of activation would not be significant if all other activations that related to awareness occurred in the same place. But they do not. If the activations relate to awareness of the self (O1, O2, and O3) then they can be found in the medial PF cortex. And there is a reason for this finding. As we explain in Chapter 3, the medial PF cortex is specialized for 'internal' signals, and other, more lateral parts of the PF cortex are specialized for external signals (Passingham et al. 2010).

A further assumption lies behind the notion of re-representation. Re-representation occurs via hierarchical processing (Chapter 8), and the higher-order representations occur more rostrally in the hierarchy. The caudal-to-rostral gradient illustrated in Figure 9.7 exemplifies this hierarchy, in which the higher-order representations (O3) lie rostral to the lower order ones (O1). As Lau and Rosenthal (2011) argue, 'self-referential conscious thinking relies on third-order representations'. By third-order representations, they refer to the re-representation of re-representations. A second-order representation is merely the re-representation of representations.

We can now apply these notions to reasoning (R1). As we mentioned earlier, Bunge et al. (2005) asked subjects to say whether 'chain-link' was analogous to 'bouquet-flower'. The subjects receive two relations: 'chain-link' and 'bouquet-flower'. But to solve the problem they have to compare the two relations. In other words, they have to represent

the relation between two relations. In this experiment, the activation occurred in a rostral part of the granular PF cortex, lying near the border of the polar PF cortex with the mid-lateral PF cortex. The region in question may correspond either to a rostral part of area 46 or to area 10, but regardless of the precise location it appears to be one that lies high in the prefrontal hierarchy. Its location on the lateral surface of the hemisphere, as opposed to the medial PF cortex, probably reflects the fact that lateral PF areas analyse lower-order representations of the relations between objects.

The activations that relate to moral and social rules (R2) differ from those just mentioned in that they occur on the medial surface. We view the relation between rostral and caudal activation sites in more-or-less the same way as just explained for the re-representation of relations. More rostral regions re-present information analysed in more caudal parts of the medial frontal cortex. As Chapter 3 explains, these areas analyse the outcomes of actions, with a specialization for ‘internal’ signals.

In the first place, children learn moral and social rules by externally imposed sanctions, such as punishment. And this requires them to learn the outcomes of actions. But the aim of socialization is to teach the child to internalize the rules in order to regulate their own behaviour (Bandura 2001). So as children learn moral and social rules, ‘internal’ signals become increasingly important. That is why, when adults consider situations in which they have deliberately flouted social norms, activation occurs in the paracingulate cortex (Berthoz et al. 2006). This activation, which lies in medial area 32 at the dorsoventral level of the genu of the corpus callosum, could reflect the guilt that regulates one’s own behaviour. And it could follow from having a representation of oneself as someone who adheres to social rules and behaves morally. The fact that activations occur in much the same area when subjects consider whether trait words such as ‘good’ or ‘kind’ apply to themselves (O3) provides some support to these ideas. This function parallels the one proposed earlier for the relation between relations. Here the re-representation also involves the relationship between two relations. One involves a relation between an act and a moral or social norm, and the other involves the relation between the self and a moral or social norm.

Error reduction and avoidance

We have deliberately left to last the activations that relate to imagining future events, also known as scenarios (E2). We mention earlier that these activations are close, anatomically, to those that occur when people recollect autobiographical memories (Hassabis et al. 2007a). When people imagine future events, they can consider the outcomes of hypothetical courses of action. In other words, they can engage in mental trial-and-error behaviour. When people imagine future events, activations occur in the polar PF cortex (Hassabis et al. 2007a), which also becomes activated when subjects consider alternative choices (Boorman et al. 2009) and the relative value of alternative choices (Boorman et al. 2011).

We said in our proposal that the PF cortex mediates fast learning. In the case of anthropoid monkeys, we argued that the granular PF cortex allowed them to learn, at the limit, in just one trial (Chapter 8). Fast learning reduces the errors that occur as monkeys adapt to a new situation. Monkeys also learn abstract rules and strategies that permit them to

limit errors without any additional learning or, as is more often the case, as they bring their fast-learning mechanism to bear on a problem. Similarly, the ability to assign causal responsibility between a choice and an outcome, based on a single event, reduces future errors (Chapter 4). Accordingly, we propose in Chapter 8 that the advantage conferred by the PF cortex concerns the reduction of errors. Given that people can simulate actions in their imagination, they can, in principle, develop a plan to avoid errors altogether.

There are other ways in which people can learn without error. First, they can act on the basis of verbal instructions and can learn facts about the world by being told them. Reading performs the same function in the visual modality. And we have reviewed evidence that activations occur in the granular PF cortex when people prepare to act according to task instructions, and also when they learn new facts.

Second, people can also learn by imitating others, and this kind of behaviour becomes important when they can discern the intentions of others. And we have shown activations occur in the PF cortex when people imitate others, for example, in making stone tools. Activations also occur in the PF cortex when people read the intentions of others.

Chapter 8 explains that the advances mediated by the primate PF cortex reduced the errors inherent in the ancestral reinforcement-learning mechanism. Thus, primates advanced from the slow trial-and-error learning used by their nonprimate ancestors. These older learning systems reduced errors by averaging over many feedback events. Chapter 8 argues that primates evolved an ability to reduce errors by using a single event to generate goals, and, when necessary, prospectively encoding them until the time comes to act.

In this chapter, we argue that sometime during our evolution humans advanced error reduction to a new level. People can learn from instruction, imitation, and mental trial-and-error behaviour. Our ancestors somehow overcame the need for physical trial-and-error behaviour and could thereby reduce its attendant risks and inevitable failures.

Imitation and instruction can prevent errors, provided that a solution to some problem is known to a member of the group. But mental trial-and-error does more than that. Trial-and-error behaviour, conducted entirely in the imagination, allows the development of alternative scenarios, complete with potential outcomes. People can try out different approaches to a problem, drawing variously on different domains of knowledge, without incurring any risk or wasting much energy. And this cognitive operation becomes all the more powerful when combined with re-representation. When these capabilities appeared during human evolution, the scenarios generated by mental time travel permitted people to play out potential plans in their imagination. And the knowledge that they used to do so depended partly on re-representations in the PF cortex. In this way, mental trial-and-error does more than reduce errors, it provides insight.

Chapter 10

Conclusions

Overview

This chapter compares our proposal with others in the literature and evaluates each of them against five tests: (1) does the proposal take into account the evolutionary history of the PF cortex?; (2) does it explain how connectional anatomy allows the PF cortex to perform the proposed function?; (3) does it specify how the function of the PF cortex differs from that of other areas?; (4) is it consistent with the broad scope of findings on the PF cortex?; and (5) is it stated precisely enough to be tested? We end by suggesting some ways of testing our proposal.

Introduction

Chapter 1 lays out the five aims, which we can now set out in fuller form:

1. To say what the granular PF cortex allows primates to do that their ancestors and other mammals do less efficiently, if at all, and to say what the expansion of the granular PF cortex in anthropoid primates allowed them to do better than other primates.
2. To say how the axonal connections of the granular PF cortex allow it, but not other areas, to provide these advantages.
3. To explain the fundamental function of the granular PF cortex, as a whole, and explain how its function differs from that of other parts of the brain.
4. To say how this function accounts for the activations observed in the human PF cortex during complex cognitive tasks.
5. To explain how our proposal differs from others in the literature and to tell readers what kinds of observations could refute it.

It is time to evaluate how well we have achieved these aims. Chapter 2 deals with the first one. It examines the evolution of the PF cortex, including some of the selective pressures that led to specific advances during primate evolution. We argue there that the evolution of the granular PF cortex occurred in stages and that these stages accompanied other advances, such as developments in vision and hand function. The eyes of early primates faced forward, and they adopted new ways of moving, grasping, and hand-to-mouth feeding. The first granular PF areas, the caudal PF cortex and the granular OFC,

appeared in these animals. The dorsal, ventral, and polar PF cortex appeared later in anthropoid primates as they became larger and had to contend with serious shortfalls in their favoured foods, not to mention competition and the threat of predation.

Chapters 3–7 deal with the second aim. These chapters explain how the connections of each major region of the primate PF cortex allow it to do what it does and why it alone can perform its functions. We examine the PF cortex region-by-region because its connections vary region-by-region:

1. Chapter 3 points to the connections of the medial PF cortex with the hippocampus, amygdala, and medial premotor areas that allow it to improve the use of ‘internal’ signals in guiding foraging choices among actions and rules for action, including an assessment of their current value with respect to the effort costs involved.
2. Chapter 4 stresses that the connections of the orbital PF cortex allow it to improve the use of external signals in guiding foraging choices, for choosing among objects. The orbital PF cortex has connections with many sensory areas, including visual, somatosensory, gustatory, olfactory, and visceral cortex. These connections permit the orbital PF cortex to develop high-dimensional conjunctions of information about specific behavioural outcomes, with emphasis on their visual features. We argue that the granular OFC assigns a specific outcome to the specific choice that seems to have caused it, based on a single event. Interconnections with the amygdala provide updated valuations of outcomes in terms of current needs.
3. Chapter 5 focuses on attention and search functions. The connections that the caudal PF cortex receives from visual areas convey signals from both low- and high-order vision and include both the dorsal and ventral visual streams. Based on corticocortical connections with these areas and corticofugal projections that control brainstem oculomotor nuclei, the caudal PF cortex can direct both overt and covert attention to potential goals of action. We argue that the caudal PF cortex (area 8), including the frontal eye field (FEF), is involved in the search for goals that result from learning—goal-oriented attention—as opposed to reflexive or stimulus-driven attention. Rather than considering the FEF as an oculomotor or a premotor area, we treat its as part of the prefrontal cortex: a part that orients attention to objects and places of learned value, including covert attention and overt attention (in the form of eye movements). In so doing, it enhances the processing of both foveal and extrafoveal information.
4. Chapter 6 stresses the generation of goals by the dorsal PF cortex, based in part on connections with the posterior parietal cortex. These projections provide information about the order, timing, and location of visual events, which establish an important part of the current behavioural context. Goal generation also depends on information from the orbital PF cortex about the outcomes associated with those goals and their current value. The dorsal PF cortex provides a mechanism for overcoming the interference caused by the memory of previous events and it seems to do so, at least in part, by prospectively coding current goals. Connections with the premotor areas provide a route by which these goals can be achieved.

5. Chapter 7 proposes that the ventral PF cortex generates goals based on a visual or an acoustic context. It can perform this function because of its connections with the inferior and superior temporal cortex, the orbital PF cortex, and the amygdala. These connections provide it with visual and auditory signs, predicted outcomes, and a valuation of that outcome in terms of current biological needs. Signs consist of intermediate levels of feature conjunction, between elemental features and whole objects. The ventral PF cortex uses the same connections to apply abstract rules and strategies and thereby transfer previous experience to a new behavioural problem.

After taking the PF cortex apart in this way, Chapter 8 puts it back together. It deals with the PF cortex as a whole, and it culminates with the fulfilment of our third goal: a specific proposal concerning the fundamental function of the primate PF cortex, with emphasis on the areas that evolved in primates. We propose that the granular PF cortex generates goals that are appropriate to the current context and current needs, and that it can do so on the basis of single events. As a result, anthropoids can solve a broad range of problems based on one or a few experiences, and they can avoid many of the errors inherent in the ancestral reinforcement-learning mechanism. We propose that in response to specific adaptive pressures, at particular times and places in primate history (Chapters 2 and 8), granular PF areas evolved to implement a new general-purpose learning mechanism, one that augments the ancestral general-purpose learning system. The ancestral system controls automatic behaviours by adjusting the strength of associations through reinforcing feedback; the primate way of problem-solving involves attentive control of behaviour—and fewer errors.

Chapter 9 deals with our fourth aim: to explain how the fundamental PF function accounts for the brain activations observed during human cognition. It stresses the power of re-representation. As a consequence, the human PF cortex can re-represent perceptual states, the intentions and mental states of others, and the relations among relations. Chapter 9 also suggests that the human PF cortex elaborates the function that the PF cortex performs in other anthropoids; just as the granular PF cortex of monkeys allows them to avoid errors through rapid learning and abstract strategies, so the PF cortex of humans allows us to avoid errors through instruction, imitation, and mental trial-and-error behaviour.

The remainder of this chapter addresses our fifth and final aim: to compare our account of the primate PF cortex with others in the literature and to suggest some ways to test it. Accordingly, the next two sections explain that other proposals either lack the evolutionary perspective that ours provides, apply to only part of the primate PF cortex, do not explain why its unique combination of connections accounts for its function, do not say what function the primate PF cortex performs that other brain areas cannot, fail to account for the broad range of behaviours to which the PF cortex contributes, or fail to generate testable hypotheses.

We divide alternative proposals into two groups, taken up in separate sections: those that depend mainly on results from monkeys and those that depend mainly on evidence from humans. Of course, proponents of the former group have also attempted to extend them to humans, and proponents of the latter group have also mentioned evidence from monkeys that they took to support their view. So we make this division merely for

convenience, and sometimes, when a theory draws on both monkey and human research, we discuss it in both sections.

We follow Wood and Grafman (2003) in tabulating the various theories and trying to assess them against a set of criteria. We use five criteria, which say that a successful theory of the PF cortex should:

1. Incorporate the evolutionary history of the PF cortex, especially the appearance of the granular PF cortex in primates and the emergence of new granular areas in advanced anthropoids: the *history* test.
2. Explain why the connectional anatomy of the PF cortex makes it possible for it to perform the proposed function: the *anatomy* test.
3. Identify the specific function of the PF cortex, in contrast to other parts of the brain: the *specificity* test.
4. Account for the broad scope of available data: the *generality* test.
5. Be stated precisely enough to be testable by feasible observations: the *falsifiability* test.

Theories based on evidence from monkeys

Our own proposal depends primarily on evidence from monkeys, and so we consider this class of ideas first. In Table 10.1, an 'X' signifies our opinion that the theory listed on that line fails a particular test. A question mark (?) indicates that the theory addresses the test, but that we are unsure about whether it does so successfully. When used for the falsifiability test, the '?' means that although some versions of that theory fail, others might pass, even if no one has yet pushed the theory in that direction. A dash ('—') means that the theory does not address the test at all.

Inevitably, filling in the tables requires subjective judgements. Consider the history test. If a theory says nothing about evolution, it could be taken to have failed that test. Yet we can sometimes see ways that a given theory could address the issue. However, some theories are simply inconsistent with an evolutionary perspective. A theory fails the history test when it posits, as the fundamental function of the primate PF cortex, some behavioural capacity that a wide diversity of nonprimate species share.

We also appreciate that the tests are not entirely independent. For example, the anatomy test assesses a theory by whether it specifies how the connections of the PF cortex allow it to do what it does. The specificity test assesses whether other areas can to do the same thing, and in doing this we sometimes take the connections into account.

We begin by discussing the working memory theory in relation to all five criteria because it has been so influential. Readers will recognize that many of the same points apply to other theories, as well. So to avoid repetition when discussing these other ideas, we concentrate on particular strengths or particular weaknesses, without necessarily addressing all the tests.

Working memory

Chapters 5 and 6 review the results that have led to a focus on working memory as the predominant, if not exclusive, function of the PF cortex (Goldman-Rakic 1987). For

Table 10.1 Theories of the PF cortex based mainly on observations in monkeys, evaluated against five tests.

Theories	History	Anatomy	Specificity	Generality	Falsifiability
Working memory	X		X	X	?
Cross-temporal contingencies	X			X	
Planning, sequences	—			X	?
Temporally extended events	—	—		X	?
Conditional learning	X		X	X	
Behavioural inhibition		—		X	
Abstractions, rules, and strategies	—			X	
Fast learning	?			X	
Hierarchical processing	—		X		
Integration	—		—		?
Adaptive coding, problem solving	—	—			?
Animal learning theory	X			X	X

X, the theory fails the test.

?, the theory is either unclear on this point or differs in various formulations.

—, the theory does not address the issue.

many years this idea dominated the literature, and proponents focused on retrospective, sensory memory. Like many other theories of the PF cortex, it derived mainly from just a few tasks, in this case mainly the delayed response and delayed alternation tasks. We understand this emphasis, given the severity of the impairment that lesions of the PF cortex cause on these tasks (Chapter 6). But we think the working memory theory fails many of the tests of a successful theory, and so we now take these deficiencies up in turn.

In considering how the working memory theory faces up to the history test, we acknowledge the seminal contribution of Preuss and Goldman-Rakic (1991a, b). Although Goldman-Rakic was a powerful and persistent proponent of the working memory theory, the comparative work that she published with Preuss provides a key insight that overturns the theory. The area upon which the archetypical working memory task depends in monkeys, a part of the granular PF cortex, does not exist in either nonmammals or in bushbabies. Yet these animals have a robust working memory capacity.

Accordingly, the working memory theory makes little sense from a comparative perspective. Chapter 1 explains that rats can perform tasks such as the radial arm maze, which require working memory, and later in this chapter we go through some of these arguments in more detail. Yet, like other nonprimate mammals, rats lack a granular PF cortex. So one would have to assume that once the granular PF cortex appeared in anthropoid primates it ‘took over’ a function that other areas had previously performed. This idea lacks both parsimony and plausibility. It should not be surprising that rats, with their sophisticated brains, can solve the simple problems posed by working memory tasks. The

finding in need of explanation is the failure of monkeys with mid-lateral PF cortex lesions to solve these simple problems. We take up that topic later.

The second test, the anatomy test, requires that the working memory theory explain how the connections of the primate PF cortex lead to its unique functions. In her principal presentation of the working memory theory, Goldman-Rakic (1987) provided an extensive review of the connections of the PF cortex, as they were known at the time. In Wilson et al. (1993), she also appealed to the connections from the parietal and temporal lobes when comparing the functions of the dorsal and ventral PF cortex.

We have suggested a reformulation of this distinction in light of the more recent evidence that the posterior parietal cortex supplies not only spatial but also timing and other inputs to the dorsal PF cortex (Chapter 6). But we agree with the idea that connections with temporal and posterior parietal cortex underlie an important aspect of PF cortex function. Finally, Goldman-Rakic also discussed how the cellular architecture of the PF cortex might support working memory (Goldman-Rakic 1995; Constantinidis et al. 2001), though these ideas do not address the anatomy test directly.

The third test is the specificity test, and as formulated the working memory theory fails to say how the PF cortex *differs* from the posterior parietal cortex. Proponents of this theory have placed great emphasis on the presence of cells in the PF cortex that have delay-period activity. Yet, as shown by Chafee and Goldman-Rakic (1998), among others, cells with delay-period activity also occur in the posterior parietal cortex. Proponents of the working memory theory could suggest that memory coding in the posterior parietal cortex depends on the PF cortex, and they could support this suggestion by pointing to the fact that cooling the caudal PF cortex leads to a decrease in the delay-related activity in the posterior parietal cortex (Chafee & Goldman-Rakic 2000). But the same experiment showed that cooling the posterior parietal cortex has a comparable effect on activity in the PF cortex, and so this argument is unpersuasive. If the theory is modified to propose that working memory depends on information circulating between the prefrontal cortex and the posterior parietal cortex, then it fails the specificity test.

The fourth test is the generality test, which assesses whether the theory accounts for all of the reliable data. Table 8.1 presents a selective list of tasks and lesion effects, and it will be seen that the working memory theory fails to account for many of the published results. For example, monkeys with ventral PF cortex lesions show impairments on the go no-go discrimination task (Iversen & Mishkin 1970), on the simultaneous matching-to-sample task (Rushworth et al. 1997a), and on conditional visuomotor tasks (Bussey et al. 2001). None of these tasks have a delay period between the presentation of the cue and the subsequent action. And yet it is clear that Goldman-Rakic and her colleagues (Wilson et al. 1993) intended the working memory theory to apply at least to the whole of the lateral surface of the PF cortex, if not to the PF cortex as a whole.

The theory also fails to account for many of the cell types that can be found in the PF cortex (Table 8.2). As formulated by its proponents, the working memory theory relies heavily on cell activity during so-called memory periods. In simple tasks, such as the oculomotor delayed response task, many cells appear to encode the memory of spatial locations. This finding is, of course, weakly consistent with the theory (Funahashi et al. 1989).

But a more carefully controlled study showed that only a minority of PF cells encode a remembered, as opposed to an attended, location (Lebedev et al. 2004). Thus, the working memory theory also fails the generality test.

Furthermore, if the theory is taken apply to the entirety of the PF cortex, it fails the generality test on other grounds, as well. Tsujimoto et al. (2010) studied cell activity in the polar PF cortex as monkeys performed the oculomotor delayed response task. They found no activity during the delay period that encoded remembered locations—or anything else. And in a study of the mid-lateral and caudal PF cortex by Genovesio et al. (2011), in which monkeys judged relative distances, very few cells encoded remembered locations, only 2–5% more cells than expected by chance. A much larger number of cells encoded other information, especially the choice among goals.

The final test is that a valid theory must be falsifiable. Here we enter a query for the working memory theory because it can be formulated in many different ways. If the theory simply refers to the ability to remember previous cues over a delay period, then it is falsifiable and it is false. But, as Chapter 1 explains, the working memory theory as first formulated by Baddeley and Hitch (1974) included a ‘central executive’, and Goldman-Rakic (1998) included the central executive in her formulation of the working memory theory. In that case, no observation could genuinely test the theory because virtually all tasks of any interest involve some sort of central executive function.

Because the working memory theory fails the generality, specificity, and history tests, we conclude that working memory is not the fundamental function of the PF cortex.

Cross-temporal contingency

Fuster (2008) has suggested that the PF cortex functions in the integration of information across a delay. He called this relationship a cross-temporal contingency because it involves integrating information across time gaps. On the delayed response task, for example, the correct choice depends on an event that occurred prior to the delay period. So the notion of cross-temporal integration and hierarchy captures this aspect of PF cortex function.

In his book, Fuster (2008) reviews the evolutionary history of the PF cortex, as he sees it. However, he deals with only a few of the issues that we have raised in Chapter 2, and we disagree with key aspects of his argument. For example, Fuster views the PF cortex of rodents, carnivores, and primates as homologous, an idea that we reject. Most importantly, Fuster does not specify the advantages that various parts of the PF cortex conferred upon the species that evolved these structures at the time that they first appeared. So Fuster’s theory fails the history test.

Fuster (2008) also reviews the connections of the PF cortex. His suggestion that the PF cortex lies at the apex of the perception–action cycle differs from our suggestion concerning hierarchies mainly in the degree of specificity and in terminology. So, in this respect, his theory says why the PF cortex can perform the functions that it does (the anatomy test) and why other areas cannot (the specificity test).

Fuster provides an extensive review of the lesion and cell-activity data, and so he tries to account for a broad range of the data. However, given that the concepts of hierarchy and ‘cross-temporal integration’ will not apply to all the data, he employs a variety of

explanations rather than putting forward a single proposal concerning the fundamental function of the PF cortex as a whole, as we do in Chapter 8. So Fuster concludes that the PF cortex functions in, for example, working memory, set, and behavioural inhibition. We enter an 'X' in the table, meaning that although he attempts to account for a broad scope of data, he does not offer a synthetic proposal beyond the invocation of hierarchy.

Planning and sequences

The theories discussed so far have stressed maintaining and integrating information over a delay period. These theories typically stress *retrospective* memory and the maintenance of sensory signals in memory. But Chapters 6 and 7 review the evidence that much of the delay-period activity in the PF cortex encodes goals *prospectively*. Prospective coding is a kind of working memory, but not the kind envisaged by the proponents of the working memory theory of the PF cortex.

Prospective coding has led Tanji and Hoshi (2008) to stress the role of the PF cortex in planning, and especially in planning of a sequence of goals. As Chapter 6 mentions, Mushiake et al. (2006) found cells that code for future steps in a sequence of movements that solve a visual-maze task.

In their review, Tanji and Hoshi cite studies from their own laboratory showing that PF cortex cells encode the abstract structure of goal sequences (Shima et al. 2007). These authors, like others, suggest a hierarchy with the PF cortex at its apex. They show, for example, that cells in the preSMA encode the temporal organization of a specific sequence (Shima & Tanji 2000). By reviewing the connections that underlie this capacity, the planning theory of Tanji and Hoshi makes some progress towards passing the anatomy test.

Hoshi (2008), following the same line, has specifically compared cell activity in the dorsal and ventral PF cortex to activity in the dorsal and ventral premotor cortex, as well as in the primary motor cortex. He further discusses the connections among these areas, and so attempts to meet the anatomy and specificity tests.

Planning involves preparing a sequence of goals. So we agree that the prospective coding of goals, goal sequences, and abstractions of goal sequences captures an important aspect of PF cortex function. But as a theory of the PF cortex a sequence-planning theory fails the generality test. The same conclusion applies to any theory that relies too much on sequences. Recall that, in monkeys, lesions of the granular PF cortex cause an impairment on simple tasks that lack a sequence of goals, such as the conditional visuomotor task (Bussey et al. 2001), the matching-to-sample task (Rushworth et al. 1997a), or the go no-go task without delays (Iversen & Mishkin 1970). A theory of the PF cortex in terms of planning sequences does not account for these results.

We acknowledge that Tanji and Hoshi (2008) have included in their proposal the idea that the PF cortex contributes to many aspects of 'executive control', including selective attention to action, the selection of an intended action, and the implementation of behavioural rules. However, their approach faces the difficulty that as one generalizes a planning theory of the PF cortex to encompass ever-more aspects of executive control, it becomes difficult to know what counts as a falsification.

Temporally extended events

Gaffan and his colleagues have argued that the PF cortex processes and represents ‘temporarily extended’ or ‘temporarily complex’ events (Browning & Gaffan 2008). Chapter 8 explains the specific experiment that first gave rise to this theory. Briefly, it involved teaching monkeys that the choice of one picture led to the presentation of another one for 2 seconds before delivery of a reward (see Figure 8.8A). In a control condition, the delay was unfilled by any stimulus on the screen. Browning et al. found that monkeys with disconnections between the inferior temporal cortex and the PF cortex had impairments in the experimental (filled delay) but not the control (unfilled delay) condition (see Figure 8.8B). Only the former condition has a series of events before the reward.

Wilson et al. (2010) argue that this theory provides an account of what the PF cortex does as a whole and that it changes the focus from vague and untestable concepts such as executive function to an important kind of representational knowledge. We agree with the latter point. We also agree that learning about sequences of events, which unfold over various time frames, captures an important aspect of PF cortex function, especially as it contributes to the context hierarchy (Chapter 8).

However, the theory clearly fails the generality test, because, as already mentioned, monkeys with PF lesions can be impaired on tasks that, by any conventional analysis, lack a sequence of events. If, on the other hand, one views all tasks as having an event sequence, then the theory becomes unfalsifiable.

Conditional learning

Both Goldman-Rakic (1987) and Passingham (1993) stressed the fact that tasks impaired by PF cortex lesions often have a conditional structure (Chapters 6–8). In conditional tasks, the correct choice depends on an instruction cue. Construed in this way, this class of task not only includes the obvious ones, such as conditional visuomotor learning and paired associate learning, but also the delayed response task. The conditional learning theory captures the fact that the PF cortex plays a key role in the flexible generation of the goals based on a current context, whether with a delay as on the delayed response task or without one as on the conditional visuomotor learning task. The theory, as formulated by Passingham (1993), addressed the anatomy test.

However, other areas are also critically involved in conditional behaviour. For example, lesions of the premotor cortex cause severe impairments on conditional visuomotor tasks (Halsband & Passingham 1985; Petrides 1987), and so do lesions in the thalamic nuclei that project to the premotor areas (Canavan et al. 1989). A full account of the primate PF cortex has to distinguish its contribution from that of other areas. Thus, the conditional learning theory fails the specificity test.

The theory also fails the generality test. It does not explain why lesions of the PF cortex lesions cause an impairment on the task described in the previous section that used temporally extended events. That is a simple discrimination task with a delay of the reward, and not a conditional task (Browning & Gaffan 2008).

Finally, the theory fails the history test because all mammals can learn conditional visuomotor tasks (Dunn et al. 2005; Dumont et al. 2007), a topic that we take up later.

Behavioural inhibition, response inhibition, inhibitory control

Several theories of the PF cortex, or some part of it, have emphasized behavioural inhibition, inhibitory control, or response inhibition (e.g. Roberts & Wallis 2000; Eagle et al. 2008). For example, patients with PF cortex lesions have impairments in suppressing a prosaccade when they need to make an antisaccade (Ploner et al. 2005), and ventral PF cortex lesions cause impairments in stopping on the stop-signal reaction-time task (Aron et al. 2003). These findings bear on the generation and cancellation of goals, but they do not indicate that the fundamental function of the PF cortex is inhibitory control.

The behavioural inhibition theory passes the history test because it holds that the PF cortex evolved to suppress automatic or prepotent behaviours, including instinctual ones. It also passes the specificity test because it says what the PF cortex does that other areas do not do.

Accordingly, the concept of behavioural inhibition has its place in our proposal. The suppression of default, habitual, or prepotent behaviours, when they have ceased producing a desired outcome, must be a part of what the PF cortex does (Chapters 3 and 8). Our proposal emphasizes the *affirmative* functions of the PF cortex, but it encompasses these negative functions indirectly by recognizing that the attentive generation of goals implies the suppression of goals generated automatically (Chapter 8). Default or prepotent behaviours, such as looking at an attention-capturing stimulus, need to be suppressed to pursue other goals, as in the antisaccade task. The PF cortex must cancel goals as well as generate them, and it must select objects and places to avoid as well as objects and places to act upon. In this sense, our proposal includes negative functions such as behavioural inhibition, but it does so implicitly rather than explicitly.

The inhibition theory fails the generality test, however, because it neglects the affirmative functions that the PF cortex performs. Expressed in terms of responses and rewards, the theory predicts that lesions of the PF cortex should cause an abnormal persistence with responses that no longer produce rewards, called perseveration. However, the evidence shows that too much persistence after an unrewarded choice occurs no more prominently than too little persistence after a rewarded choice.

For example, Milner (1963) stressed her observation that patients with frontal lobe lesions make perseverative errors on the Wisconsin card sorting task. And Mishkin (1964) picked up this idea when he proposed that PF cortex lesions cause a ‘perseveration of central sets’. But such patients also make random errors (Barcelo & Knight 2002). They fail to *stay with* a rule that produces positive feedback (inadequate persistence), in addition to failing to *shift from* a rule that produces negative feedback (perseveration).

Reversal tasks can also test the behavioural inhibition theory, which predicts that PF cortex lesions should mainly increase errors after unrewarded trials (negative feedback). Results from the action reversal task contradict this prediction (see Figure 3.8). Whereas normal monkeys stay with a rewarded action, monkeys with lesions of the medial PF cortex do so less often (Kennerley et al. 2006; Rudebeck et al. 2008). Likewise, on the object reversal task (see Figure 4.8), monkeys with orbital PF cortex lesions use positive feedback inefficiently but use negative feedback almost normally (Rudebeck & Murray

2008). Camille et al. (2011) studied patients with comparable lesions and confirmed these findings for both tasks (see Figure 4.9).

The conditional visuomotor task can also test the behavioural inhibition theory. Chapter 7 explains that some monkeys spontaneously adopt the ‘change-shift’ and ‘repeat-stay’ strategies while performing this task (Wise & Murray 1999). If the PF cortex functions predominantly in suppressing previous responses, then PF cortex lesions should not cause an impairment in the ‘stay’ strategy. Staying with a previously rewarded response should benefit from a lesion that causes perseveration. In fact, Figure 8.6 shows that monkeys with combined lesions of the ventral and orbital PF cortex show equal (and severe) impairments in both the ‘stay’ and ‘shift’ strategies. The inhibition theory also predicts that PF cortex lesions should spare perseverative, overlearned conditional visuomotor associations, also known as stimulus–response (S–R) associations or habits (Chapter 3). Combined lesions of the ventral and orbital PF cortex cause a severe impairment, however (Bussey et al. 2001).

Also according to inhibition theory, the high-volatility condition in the three-arm bandit task (see Figures 4.5 and 4.6) should lead to large impairments after orbital PF cortex lesions. Lesioned monkeys should perseverate on previous choices rather than changing their choices in a flexible way. Yet lesioned monkeys ‘track’ or ‘match’ volatile reward probabilities normally (Walton et al. 2010).

The reversed reward contingency task provides a direct test of the behavioural inhibition theory. On this task, the choice of a smaller amount of food yields a larger amount and vice versa. According to the theory, lesions of the PF cortex should cause an impairment in suppressing the prepotent response: reaching to the larger amount of food. In fact, lesions of the orbital PF cortex have no effect on learning this task (Chudasama et al. 2007).

Proponents of the theory could argue that, notwithstanding all of this contradictory evidence, other results appear to support it. The go no-go discrimination task provides one example. On this task, one object instructs a monkey to make a ‘response’ and another object instructs the animal to withhold any response. Monkeys with lesions of the ventral PF cortex tend to ‘go’ incorrectly on ‘no-go’ trials (Iversen & Mishkin 1970), called errors of commission. At first glance, this result seems to reflect an impairment in suppressing inappropriate responses. Yet in the task used by Iversen and Mishkin only correct ‘go’ trials yielded a reward, and this means that ‘going’ becomes the default response. Without specific control procedures, monkeys develop a strong ‘go’ bias on ‘no-go’ trials in order to get to the next ‘go’ trial faster and therefore their next opportunity to obtain a reward.

McEneaney and Butter (1969) overcame this flaw in the go no-go task by testing monkeys on a series of reversals, which established a condition in which ‘not going’ became the default response to a stimulus. After the experimenters established that default behaviour, monkeys with lesions of the OFC were slow to ‘go’ after the next reversal. Collectively, the results from go no-go discrimination tasks show that lesioned monkeys *change* their behaviour abnormally slowly, but they do not support an interpretation in terms of

response suppression. Instead, these results stress an affirmative function of the PF cortex: fast learning (Chapter 8).

Jones and Mishkin (1972), who made combined lesions of the orbital and ventral PF cortex, defined perseveration as a longer series of trials with a below-chance level of performance after a reversal. They found what they expected, and proponents of the behavioural inhibition theory often cite this finding. However, Bussey et al. (2001) made the same lesion and found a severe impairment in both fast learning and in the application of abstract strategies, such as 'lose-shift'. And Izquierdo et al. (2004) observed that monkeys with orbital PF cortex lesions failed to develop a reversal learning set. Chapter 8 explains that fast learning, abstract strategies, and reversal set all require the use of a single event to generate a goal. Viewed in this light, the results obtained by Jones and Mishkin provide no support for the behavioural inhibition theory that they do not also provide to the affirmative proposal advanced in Chapter 8.

Another result that appears to support the behavioural inhibition theory involves marmoset monkeys. Lesions of the ventral PF cortex cause impairments on the extradimensional shift task (Dias et al. 1996). Chapter 7 explains that on this task monkeys must shift to a new rule about which stimulus dimension is relevant to a choice between two novel stimuli (see Figure 7.10). Dias et al. interpreted their results in terms of a failure to suppress choices based on the previous rule, which they called attentional set. However, the effect of PF cortex lesions does not persist: the animals performed normally on a second extradimensional shift after learning the first one (Dias et al. 1997). These results therefore seem to reflect the affirmative function of fast learning, especially in novel circumstances, rather than an impairment in rule suppression.

Finally, results from extinction tasks have also been cited in support of the behavioural inhibition theory (Butter 1969). Monkeys with lesions of the orbital PF cortex continue to 'respond' to stimuli longer than normal monkeys, once these actions no longer produce rewards (see Figure 4.4). An impairment in fast learning also accounts for this result.

Because it fails the generality test, we can reject the behavioural inhibition theory without denying an important role for the PF cortex in suppressive functions. Beyond that, the findings often cited in support of that theory agree as much with the proposal that monkeys use events to reduce errors through fast learning and abstract strategies (Chapter 8): an affirmative function rather than a negative one.

Abstractions of categories, rules, and strategies

Miller and his colleagues have suggested that the PF cortex represents both abstract categories (Miller et al. 2003; Roy et al. 2010) and abstract rules (Miller & Buschman 2008). The original evidence comes from the studies of Freedman et al. (2002) on visual categorization, of Nieder et al. (2002) on number, and of White and Wise (1999) and Wallis et al. (2001) on abstract rules. In parallel, Genovesio et al. (2005) have stressed the role of the PF cortex in representing abstract strategies.

We have incorporated these data into our proposal, in part by appealing to the notion of abstraction in explaining hierarchical processing. And it is the position of the PF cortex

in the context, goal, and outcome hierarchies that explains what it can do and other areas cannot.

But a pure abstraction theory of the PF cortex does not pass the generality test. For example, as mentioned earlier, monkeys with ventral PF lesions show impairments on a simple go no-go task with no delay (Iversen & Mishkin 1970), which deals with concrete stimuli and responses. They also show dramatic deficits on simple conditional visuomotor mappings, also with no delay, and even after they have become automatic through extensive training (Bussey et al. 2001). These conditional visuomotor tasks depend on concrete stimulus-response associations that involve specific stimuli and specific actions. The monkeys have experienced these mappings repeatedly in the both the recent and remote past. They do not depend on abstract rules, strategies, or categories.

Furthermore, evidence from imaging shows that the PF cortex plays a role in generating both concrete and abstract goals. Rowe et al. (2008) specifically compared activations related to the selection of a concrete finger movement and to the selection of an abstract rule. The peak of the activations in the mid-lateral PF cortex did not differ for these two tasks.

Fast learning

Miller and his colleagues have tested the ability of macaque monkeys to learn rapidly. They have taught rules (Miller & Buschman 2008), cue-response associations (Cromer et al. 2011a), and new categories (Antzoulatos & Miller 2011). They have also compared the relative time at which the cells in the PF cortex or striatum encode a choice (Miller & Buschman 2008; Antzoulatos & Miller 2011).

It will be obvious that Miller and his colleagues treat rapid learning as of particular interest, and we share that interest. We have, however, approached the issue in a different way, showing that lesions of the granular PF cortex prevent rapid learning (Chapter 8). Our proposal differs in stressing the importance of learning by single events and linking PF cortex function to other ways of reducing errors, such as the application of abstract rules and strategies.

On its own, the fast learning theory fails the generality test. Chapters 7 and 8 explain that a key function of the granular PF cortex involves the application of abstract behaviour-guiding strategies. Monkeys must learn these strategies, but once learned they simply need to apply them to the problem at hand. A fast learning theory does not account for impairments on strategy tasks, nor does it account for other impairments that follow PF cortex lesions, such as that on the delayed response task.

Miller and his colleagues do not specifically address the history test, although they could do so. We therefore enter a query on this point.

Hierarchical processing

Our proposal says that the granular PF cortex sits at the apex of context, outcome, and goal hierarchies. Others, of course, have stressed the importance of hierarchies in the PF cortex. Some of these theories derive from studies of humans (Koechlin et al. 2003; Badre 2008), but the idea originated with Jones and Powell (1970) who based it on corticocortical

connections in monkeys. This idea has influenced several theories about the PF cortex, which generally point to a progressive increase in abstraction as one moves more rostrally within the PF cortex (Badre 2008). Hierarchy theories differ, however, in their emphasis. Some point to domain generality (Wilson et al. 2010), others to relational integration (Wendelken et al. 2008), and still others to the complexity of the factors that generate a goal choice and to the time horizon involved (Summerfield & Koechlin 2009). Any theory of the PF cortex can incorporate the concept of a hierarchy.

As Chapter 8 mentions, Fuster (2008) has emphasized the idea that the PF cortex sits at the top of a perception–action hierarchy. His theory postulates a series of routes to action, with the PF cortex forming the most indirect one. However, Fuster does not specify the differences between PF cortex function and that of the posterior parietal cortex, which also participates in perception–action mappings. As a result, his theory fails the specificity test. Simply referring to a hierarchy does not explain what the primate PF cortex does that other parts of the brain do not do, except that these other areas operate at a lower hierarchical level.

Our proposal specifies that its location at the apex of a processing hierarchy allows the granular PF cortex, uniquely, to integrate all of the information needed to generate goals from a current context and events, based in large part on knowledge about specific outcomes and their current value. The PF cortex then provides the spatial goal to the premotor cortex, which computes a motor plan in order to achieve the goal. As Chapters 7 and 8 explain, the inferior temporal cortex does not have the specific outcome information needed to generate a goal, and it does not project directly to the premotor cortex. So, in contrast to the inferior temporal cortex, the granular PF cortex has all of the connections needed: access to the premotor cortex, object and cue information from the temporal visual areas, inputs from the hippocampal system that encode events, and outcome information about the visual properties of foods and fluids, as well as their updated biological value (Chapter 4).

The same sorts of arguments apply to the posterior parietal cortex, the premotor cortex, the remainder of the temporal cortex, and the hippocampus in various combinations. Fuster does not say, in each case, how the function of these areas differs because of their lower standing in the perception–action hierarchy. Our proposal specifies the difference: the granular PF cortex has all of these necessary connections and other areas do not.

Integration

Miller and Cohen (2001) have stressed, as does our proposal, that the PF cortex integrates information from all sensory domains in order to select future goals. Their theory resembles our proposal more than others in the literature. In their review, Miller and Cohen draw both on monkey research and on imaging research in humans. So we take up their ideas again in the section on human studies. Here we focus on the aspects that come primarily from monkey research.

Evidence that the PF cortex plays an integrative function in monkeys comes from experiments such as the one by Rao et al. (1997), who showed that cells in the PF cortex

integrate visual information from both the dorsal and ventral visual streams. These cells encode both spatial and nonspatial visual information when each kind of representation serves as a goal of action.

While we acknowledge similarities of their ideas with ours, the proposal as put forward in the paper by Miller and Cohen (2001) does not tackle either the history or specificity tests. A successful theory should explain why the primate PF cortex has evolved to do what it does or why its connections determine how alone can do that. We see nothing in their proposal, however, that would preclude its elaboration to address these key issues.

We enter a query for the falsifiability test because the invocation of integrative function, like executive function, can be so vague as to preclude testing.

Adaptive coding, general problem solving

Duncan (2001) has suggested that it may be wrong to look for a single, fundamental function for the PF cortex, as we have. Instead, he suggests that the PF cortex may contribute to a wide variety of cognitive functions, especially as tasks become difficult.

Much of Duncan's proposal, which he calls the multiple-demand theory, depends on data from humans, and so we defer a more thorough consideration of his idea to the next section. But in support of his theory he cites evidence from cell-activity studies of monkeys, which show that a high proportion of cells show task-related activity in a wide variety of tasks. And we know that experience with particular categories changes the representation of categories in the PF cortex (Roy et al. 2010), to cite but one example of what Duncan has called adaptive coding. Gaffan (2002) has also proposed that the PF cortex may be regarded as a general-purpose problem solver.

However, it remains to be shown that the cells in the PF cortex have more adaptability than cells in other parts of the brain, such as the posterior parietal, temporal, or hippocampal cortex. They might, but all parts of the cortex 'learn', in some sense, so no one area has a monopoly on adaptive coding. They differ in what they learn about, and in some other ways too, but the absence or paucity of adaptive coding outside of the PF cortex remains to be demonstrated.

Nevertheless, both Duncan and Gaffan advance several valuable ideas. The concept of adaptive coding, general problem-solving, and cross-domain processing capture something important about the granular PF cortex and its fundamental function. We view our proposal as consistent with these ideas, but believe that it is more specific and complete, partly because it addresses the evolution of the PF cortex and partly because it explains why the connectional anatomy of the PF cortex determines what it does. In other words, our theory passes the history and anatomy tests, but the writings of Duncan and Gaffan address neither.

Perhaps the general problem-solving and multiple-demand theories could pass these tests if developed toward that end. In our proposal (Chapter 8), we stress the ideas that the granular PF cortex serves as an adaptation for error reduction and that many of its areas evolved at a particular time and place in the history of our lineage. For example, we propose that the ventral PF cortex, the dorsal PF cortex, and probably the polar PF cortex evolved as anthropoid primates increased in size and came to depend on food resources

in particularly volatile and competitive foraging environment. As we say earlier in this chapter and in Chapter 8, our proposal suggests that the evolution of the granular PF cortex provided monkeys with a phylogenetically new general problem solver to go along with the older general-purpose learning system that relies on the slow adjustments of associations based on reinforcing feedback.

Animal learning theory

In addition to the theories addressed so far, there is another, more general idea about animal learning that could be used to account for the fundamental function of the primate PF cortex. Animal learning theory holds that all learning results from establishing and modifying associations among stimulus, responses, and outcomes. We call this the ancestral reinforcement-learning system, and we propose that the primate PF cortex evolved principally to augment it. The old general-purpose learning system evolved early in the history of animals and served them well. Indeed, the power of the ancestral general-purpose learning system explains why animals other than primates can get along so well without a granular PF cortex.

If all learning depends on associations among stimuli, responses, and outcomes, then all PF-mediated learning must also relate to associations among stimuli, responses, and outcomes. According to this view, animals differ little in their behavioural capacities except in sensory processing, generalization, and varying degrees of associative complexity. This theory addresses the specificity test by saying that the contribution of the primate PF cortex comes from the kind of integrative function that Chapter 8 discusses. In general terms, animal learning theory holds that the PF cortex allows primates to do the same things that other animals can do, only better. The evolution of trichromatic vision in catarrhine primates, for example, allows finer colour discriminations in a certain spectral range compared to other mammals. Otherwise, according to animal learning theory, pigeons, pigs, and people all learn in the same way.

As applied to PF cortex function, animal learning theory fails the falsifiability test. Put somewhat differently, because animal learning theory is unfalsifiable, its application to the PF cortex is, likewise, unfalsifiable. Although any behaviour can be described in terms of stimuli, responses, and outcomes, this does not mean that all animals learn associations among them through the same learning mechanisms. Indeed, the ability to apply those concepts to a behaviour says nothing about the underlying learning mechanisms.

Furthermore, animal learning theory fails the history test because it cites a function that evolved long before the appearance of either the agranular PF cortex in mammals or the granular PF cortex in primates.

There are, however, two aspects of animal learning theory that we have adopted. Chapter 3 explains that, in rats, certain lesions in the medial PF cortex lead to impairments in outcome-directed behaviour, but leave habitual actions intact. Lesions of other parts of the medial PF cortex have the opposite effects. Thus, as we argue in Chapter 3, the first PF areas to evolve in mammals—the agranular PF areas—regulate the behaviours acquired through the ancestral reinforcement-learning mechanisms. One can therefore view the agranular PF cortex as an intermediate stage between complete reliance on the

reinforcement-learning system in the ancestors of mammals and its later augmentation by the granular PF cortex in primates.

Second, like Balleine and his colleagues, we also distinguish between actions that require attentive processing and those that do not. Chapter 8 argues that the PF cortex becomes engaged during the attentive generation of goals. We differ from the animal learning theorists, however, in rejecting the equivalence of outcome-directed behaviour with the attentive control of behaviour. Indeed, Balleine and O'Doherty (2010) go so far as to classify all behaviour into either habits or outcome-directed behaviour, which they call goal-directed behaviour. And they apply this idea to humans.

Yet, many outcome-directed behaviours occur without attention to them. Sequential behaviours have been studied extensively, but perhaps the most instructive example involves the kind of learning favoured by animal learning theorists: stimulus-response-outcome (S–R–O) associations.

Johnsrude and her colleagues (2000) studied healthy people and patients with lesions of the orbital PF cortex or the amygdala. The subjects directed their attention toward a task that required them to count the number of red dots that appeared at various chosen places in a given run of trials. Sometimes black dots appeared instead. Along with a black or red dot, a visual pattern appeared, and when the dot was red the subject could then obtain a reward: a candy or a raisin. Unbeknownst to the subjects, the various patterns were associated with reward either 10%, 50%, or 90% of the time. Later, subjects showed that they had been instrumentally conditioned to choose high-value patterns over low-value ones, although they had no awareness of why they had made their choices. That is, they had inattentively learned the S–R–O associations that underlie outcome-directed behaviour. Interestingly, the subjects concocted completely irrelevant reasons for their choices, saying things like ‘the pattern looked interesting’. This finding shows that there is more than one kind of outcome-directed behaviour. In this sense, animal learning theory fails the generality test because it cannot account for these different kinds of outcome-directed behaviour.

Summary

None of the theories just surveyed have addressed the evolution of the PF cortex in the way that Chapter 2 does. Although the proponents of some of the theories review the connections of the PF cortex, they rarely do so in order to show why only the PF can do what it does, as we do in Chapters 3–8. Many theories do not explain what the PF cortex does that differs from other parts of the cerebral cortex, as we do. Other theories cannot account for important findings. And some of the theories are so general that they cannot be falsified.

Theories based on evidence from human subjects

Table 10.2 lists the theories that depend, for the most part, on studies of humans, evaluated against the same criteria used in Table 10.1. None of the theories specifically addresses the history test, except in a perfunctory way that compares monkeys and humans

Table 10.2 Theories of the PF cortex based mainly on observations in humans, as evaluated against five tests.

Theories	History	Anatomy	Specificity	Generality	Falsifiability
Monitoring	X	?		X	
Active maintenance of items in memory	X	X	?	X	
Executive control, maintenance of goals	—				
Episodic control	?	?			
Manipulation of items in memory	—	X		X	
Attentional selection	—			X	
Attentive retrieval	X	X		X	
Structured event knowledge		X		X	
Supervisory attention system	—	X	X		?
Multiple demands, global workspace, general intelligence	—		X		?

X, the theory fails the test.

?, the theory is either unclear on this point or differs in various formulations.

—, the theory does not address the issue.

without reference to their common ancestors. We have taken the liberty, however, of noting where the proposed function cannot, even conceivably, pass the history test.

Monitoring

Petrides (1994) has argued, as we do, that the working memory theory fails to capture the fundamental function of the PF cortex. Instead, he and his colleagues have put forward a two-stage model for the role of the PF cortex (Owen et al. 1996a). One part of the theory holds that the mid-lateral PF cortex functions in monitoring items in memory, and the other part proposes that the ventral PF cortex controls the nonautomatic retrieval of items from long-term memory.

The notion of monitoring comes from the ordered object tasks, also known as the self-ordered or subject ordered task. In the pictorial version of the task as given to people, the subject has to point to the pictures in any order that they choose, with the single rule that they must not point to the same picture twice on one trial. This rule means that the subject has to build up a memory of the pictures that they have been chosen so far, in order to identify those still available for a current choice. And Petrides has suggested that this process involves monitoring the list of items in memory.

The term monitoring can also be applied to the *n*-back task. As in the ordered object task, the subjects see or hear a list of items, such as letters, and they have to monitor them for their position in a series. Thus the monitoring of items in memory differs from the maintenance of items in memory in that the items are marked or distinguished in memory in some way. In our view, what is critical is that all of these tasks involve order.

No formulation of this theory has addressed the history test in any serious way, but Champod and Petrides (2007) have tried to address the issue of specificity. They claimed that the mid-lateral PF cortex functions in monitoring, whereas the posterior parietal cortex functions in the manipulation of items in memory.

There are two problems with this interpretation. First, the imaging data revealed activation in both areas in both conditions, although to different degrees. Second, Postle et al. (2006) applied rTMS over the PF cortex, and this temporary lesion disrupted the manipulation of items in memory. Thus, the monitoring theory fails the generality test.

As formulated, the theory addresses the anatomy test in that it accounts for the two stages of PF cortex function—monitoring and retrieval—in terms of connectivity. But it does not, as our proposal does, explain why the connections of the PF cortex determine what it, uniquely, can do. Nothing about the connections of the mid-lateral PF cortex allows one to distinguish between monitoring or manipulating items in memory. So we enter a query for this test.

Active maintenance of items in memory

Ungerleider (1995) proposed that the mid-lateral PF cortex functions in the active maintenance of information. Sakai et al. (2002a) adopted this term to account for the effect of delay-period activation in the mid-lateral PF cortex in protecting spatial items from distraction. And discussions of the functions of the PF cortex commonly invoke this concept (D'Esposito 2007).

To have any value, the term active maintenance must contrast with passive maintenance, that is, a kind of memory maintenance that does not make demands on attention. Dual-task paradigms can manipulate attention to test this distinction. For example, subjects make errors in remembering a series of letters or digits if they must engage in another task that involves articulation, which disrupts rehearsal in the 'phonological loop' (Baddeley 1986). In the same way, one can interfere with rehearsal of spatial items by requiring subjects to make saccades to irrelevant targets, which disrupts the items held in the 'visuospatial scratchpad' of working memory (Guerard et al. 2009). In either case, memory suffers because of interference with the demands of the competing task. Thus the maintenance can be said to be *attentive* or *active*.

We accept that in people the PF cortex may contribute to the active rehearsal of items in memory, and Chapter 6 presents an account of that rehearsal. However, as a theory of the PF cortex, the active-maintenance theory fails to account for much of the data. It focuses narrowly on the same kind of observations as the working memory theory and thus fails the generality test. Indeed, the active maintenance theory differs little from the working memory theory and thus fails the same tests. Earlier, we explained that PF cortex lesions in monkeys cause impairments on many tasks that make little, if any, demands on active maintenance or working memory. Furthermore, many well-known impairments after PF lesions have nothing to do with active maintenance, such as impairments in word recall or the retrieval of episodic memories.

For the specificity test we enter a query. The theory proposes that the PF cortex, but not, for example, the posterior parietal cortex, is critical for active maintenance. But it does not provide a cogent account of such differences.

Executive control and the maintenance of goals

In their theory of the PF cortex, Miller and Cohen (2001) reject the working memory theory as we do. We discuss their theory again here, in addition to the earlier discussion in the section on monkeys, because it relies heavily on the Stroop task as applied to human subjects. Miller and Cohen propose that the PF cortex functions in ‘the active maintenance of patterns of activity that represent goals and the means to achieve them’. The theory suggests that the PF cortex exerts executive control over other areas by exerting a top–down bias. Miller and Cohen do not stress the *generation* of goals, as our proposal does, but one can read that idea into their treatment of the literature.

On the Stroop task, the subjects see words such as ‘red’ spelled in blue ink. In one condition, they simply need to read the word aloud, and in the other they need to report the colour of the ink. In the second condition, the automatic or prepotent response is to say ‘red’, thus reading the word, which is incorrect. As Miller and Cohen say, in the Stroop condition the subject has to keep in mind the rule, that is, to report the colour of the ink, and this requires more attention than does merely reading the word. MacDonald et al. (2000) found activation in the mid-lateral PF cortex when the subjects prepared to report the ink colour, but not when they prepared to read the word that the ink spells (the automatic response).

In the Stroop task, the representation of the rule is maintained in memory, either for reading the word or reporting the colour of the ink. Miller and Cohen suggest that the PF cortex exerts a top–down bias on lower-order mechanisms according to the task required, and we review evidence in Chapter 5 for such a bias.

It will be clear that the theory advanced by Miller and Cohen (2001) resembles our proposal in many ways (Chapter 8). Indeed, we rely on much of the same evidence and so one would expect considerable similarity.

Nevertheless, we note some important differences. First, our theory firmly places the granular PF cortex in a comparative perspective; the theory proposed by Miller and Cohen does not. Second, our proposal emphasizes the use of single events to guide behaviour. We suggest that this capability provides one of the key adaptive advantages that the PF cortex confers upon primates, a point that Miller and Cohen do not address, at least not directly. And we separate the representation of goals, a prefrontal function, from the means of achieving them, which we ascribe to the premotor cortex.

Episodic control

Koechlin and Summerfield (2007) contrast what they call contextual control and episodic control. Contextual control refers to the specification of the appropriate action by a particular context. Episodic control refers to the modification of that control because of rules that apply for a particular episode or event. For example, assume that in the context of being in someone else’s house, a person is reluctant to answer the front door when someone knocks. If the home owner had previously asked that person to answer the door, however, this (asking) event would set up a temporary rule and the person would act differently than dictated by the context per se. Koechlin et al. (2003) reported activation in the PF cortex during episodic control, with the peak activation near the border between the dorsal PF cortex and the ventral PF cortex.

The term episodic, in this case, refers to an event that causes a rule to be stored in memory, and this usage differs from the use of the term event in Chapter 8, which views an events as what the subject did and what happened as a result. Thus, the notion of episodic control resembles that of the active maintenance of a goal or rule in memory, as Miller and Cohen suggest (2001).

However, Summerfield and Koechlin (2009) have developed their proposal further. They suggest that there is a caudal-to-rostral hierarchy along both the lateral and medial parts of the PF cortex, which relates to differences in the time over which a context is specified or a values assessed. Grafman and his colleagues (Krueger et al. 2007) have made a similar suggestion, in terms of event frequency. In Chapter 9, we take a different view of the caudal-to-rostral hierarchy within the PF cortex. We interpret this hierarchy in terms of re-representation without invoking differences in the time-frame. Of course, many parallel hierarchies could coexist in the PF cortex, and it is possible that long time horizons arise through re-representation.

The episodic control theory does not address the history test. However, it could be elaborated to do so, suggesting as we do that additional layers are added as new areas evolve. It also fails to address the anatomy test, although perhaps some future formulation will do so.

Manipulation

Postle et al. (1999) introduced the term manipulation to account for their observation of delay-period activation in the mid-lateral PF cortex when subjects re-order items in memory. The subjects were presented with five letters, and in the manipulation condition they had to re-order them in alphabetical order during the delay period. On this basis, they have advanced a manipulation theory of the PF cortex.

In our view, however, their results could reflect a dependence on processing order information rather than the manipulation of items in memory. In Chapter 6, we suggest that activation occurred in the mid-lateral PF cortex when the order of items, whether spatial or nonspatial, was critical for the performance of a task. The *n*-back task serves as one example. We also reviewed evidence for activation in this area when people generate a novel order among stimuli.

Solving reasoning problems can also be said to involve the manipulation of the items in memory rather simple maintenance. And we accept that activation occurs in the mid-lateral PF cortex when people engage in analogical reasoning (Prabhakaran et al. 1997). In tasks of this kind, such as Raven's progressive matrices task, the subjects see all of the test items as they try to solve reasoning problems, and therefore the task places a minimal load on sensory short-term memory. But, as with the tasks used by Postle and D'Esposito, problems of the sort involve sequences, and therefore order. In this case, spatial order is particularly important.

The manipulation theory fails the generality test, however. Activations can be found on tasks that do not necessarily involve manipulation. For example, we know from Pochon et al. (2001) that delay-period activation occurs in the mid-lateral PF cortex when subjects prepare to recall spatial items, even though they do not need to manipulate the items in memory because they will later recall them in the order presented.

The manipulation theory of the PF cortex also fails the anatomy test because it puts forward no anatomical account of how manipulation can occur and, like the other theories that derive from research on humans, it does not address the history test.

Attentional selection

Passingham and Rowe (2002) made a specific proposal concerning executive function, one that is related to monitoring. They suggested that the mid-lateral PF cortex functions in attentional selection. In their first experiment (Rowe et al. 2000), human subjects saw cues in three locations, which they had to remember. After a delay period, a line appeared and the subjects had to move a cursor to the remembered cue location that the line passed through. To perform this task, the subjects had to select among the three locations in memory. Passingham and Rowe proposed that they did so by using attention to enhance the representation of the relevant location in memory.

The concept of attentional selection closely resembles that of monitoring items in short-term memory. Both involve marking or accentuating some representations, among others. The term attentional selection has the advantage that, in addition to sensory information, it also applies to the generation of goals and the actions needed to achieve them. When, for example, subjects need to generate a sequence of finger movements, they can do this by attending to one of the keys, to one of the fingers, or to the locations of the keys and fingers.

Despite its strengths, the attentional selection theory fails the generality test. As Goldman-Rakic and Leung (2002) pointed out, activation occurs in imaging studies at recall even if the subjects do not need to make a selection among items in memory. In their imaging study, Leung et al. (2005) tested the memory for a set of spatial items by simply asking whether a probe item was in the set. This task does not require attentional selection of the items in memory, only the recollection of a set of locations in its entirety. We do not dispute that the mid-lateral PF cortex functions in attentional selection among items in memory, and indeed Chapter 6 makes much of this idea. But because this theory does not pass the generality test, it cannot account for the fundamental function of the PF cortex. The authors did not address the history test.

Attentive retrieval

The theories of monitoring, active maintenance, manipulation, and attentional selection all concern items in short-term memory. They differ in whether they propose that the PF cortex maintains the items in memory, monitors them, selects among them, or manipulates them. However, all of these theories fail the generality test in view of evidence that the PF cortex also functions in the retrieval of information from long-term semantic or episodic memory. Semantic memories consist of facts about the world and episodic memories involve autobiographical events in the past.

When subjects retrieve words or other semantic knowledge from memory, activation occurs in the caudal part of the ventral PF cortex. Thompson-Schill and her colleagues (Novick et al. 2009) have suggested that the retrieval involves selecting among the neural representations of competing words. Badre and Wagner (2002) have suggested instead

that it involves what they call attentive retrieval. In fact, the two proposals are closely related because competition among items in memory will lead to the requirement for attentive retrieval.

An activation occurs more rostrally in the ventral PF cortex when subjects are tested for source memory (King et al. 2005). Kostopoulos and Petrides (2008) have specifically proposed that this mid-ventral PF cortex functions in the nonautomatic (attentive) retrieval of items from long-term memory.

These findings, however, concern only part of the PF cortex and not the whole. Petrides (2005) acknowledges this limitation by contrasting the functions of the mid-lateral PF cortex and the mid-ventral PF cortex. An attentive retrieval theory thus fails as a proposal of what the PF cortex does as a whole. On these grounds, it fails the generality test. It also fails the history test because it ascribes a function to the PF cortex that nonprimate mammals can perform: retrieval of competing items from long-term memory. The invocation of ‘attention’ does not, in itself, provide sufficient precision to pass this test. And the attentive retrieval theory fails the anatomy test because it does not explain how the connections of the PF cortex allow it alone to perform this function.

Structured event knowledge

Wood and Grafman (2003) have suggested that it may be unhelpful to view the PF cortex in terms of cognitive *processes* such as working memory, adaptive coding, attention, or retrieval. They pointed out that theories about other brain regions usually concern the knowledge that is represented there. For example, parts of the temporal cortex represent semantic knowledge, and the perirhinal cortex encodes, stores, and represents knowledge about objects,

Wood and Grafman therefore suggested that we need a *representational* theory of the PF cortex, one that addresses the knowledge that the PF cortex encodes, stores, and represents. They proposed that the PF cortex represents structured event knowledge, with different subareas representing different types of such knowledge. For example, they suggest that the dorsal PF cortex represents event sequences, as in planning, and that the ventromedial PF cortex represents social rules, as they unfold during a series of encounters. This theory has several strengths. It seeks to explain the PF cortex as a whole and attempts to account for a broad range of data.

However meritorious, we do not accept the idea that representational knowledge, alone, explains PF cortex function. Both representational knowledge and cognitive processes make important contributions to the fundamental function of the PF cortex. The properties of artificial neural networks illustrate this point. The network shown in Figure 10.1 simulates the abstract strategy task of Genovesio et al. (2005), which Chapter 7 explains in detail. Like all three-layer networks, it has an input layer, an output layer, and a hidden layer. As inputs, it receives a signal that encodes the previous goal (left, right, or up), the previous cue (A, B, or C), and the current cue (also A, B, or C). The hidden layer maps the inputs to the output, which represents the current goal (left, right, or up). When the network performs this mapping, it produces an output and thus generates a goal, which simulates a cognitive *process*. But the synaptic weights that generate this goal

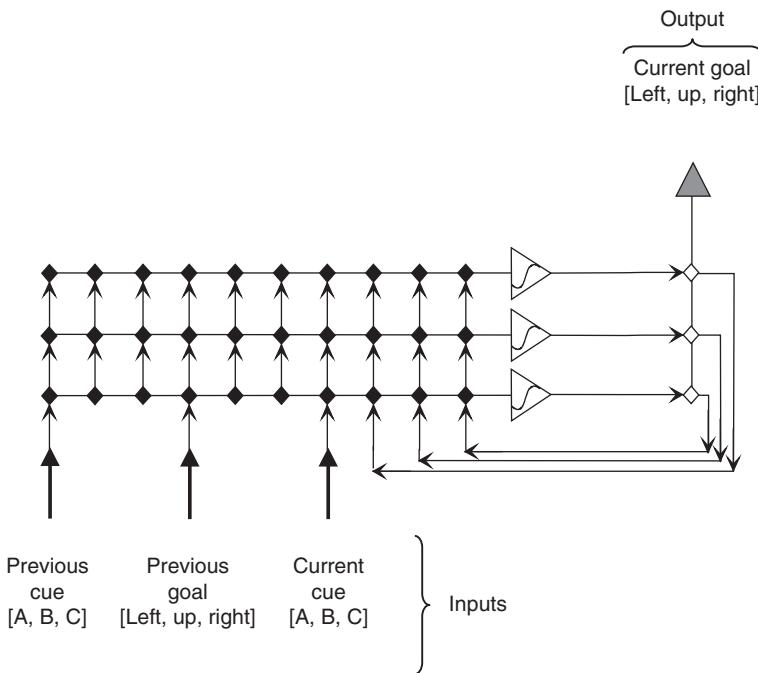


Fig. 10.1 An artificial neural network that implements the ‘repeat-stay’ and ‘change-shift’ strategies. Each black diamond represents a simulated connectional weight going from the input layer to the middle layer of the network. Inputs provide the previous cue, from a set of three cues [A, B, C], the current cue from the same set, and the previous goal, from a set of three goals [left, up, right]. The triangles containing logistic functions symbolize three of many middle-layer cells. Although not illustrated, all of these middle-layer ‘cells’ connect with all of the others. Each white diamond represents a connectional weight between the middle layer and the output layer, symbolized by a single ‘cell’ (grey triangle). The output represents one current goal from the same set of locations that serves as the previous goal. Adapted from Moody SL, Wise SP. 2000. A model that accounts for activity prior to sensory inputs and responses during matching-to-sample tasks. *Journal of Cognitive Neuroscience* 12:429–48, © 2000 by the Massachusetts Institute of Technology.

correspond to a representational *knowledge* of the ‘repeat-stay’ and ‘change-shift’ strategies. The network both has knowledge and executes a process.

So we differ from Wood and Grafman in stressing that a complete understanding of the PF cortex requires knowing about both its cognitive processes, such as goal generation, and its representational knowledge, such as context–goal mappings, abstract rules, and strategies. The danger of emphasizing one at the expense of the other is that it leads to failure on the generality test. The theory also fails the anatomy test because it does not say how connections explain the unique function of the PF cortex in structured event knowledge.

Nonetheless, our proposal agrees with many aspects of their theory. Both their theory and ours stress the importance of events, sequences of contexts and goals, hierarchies,

abstractions, and integration. Furthermore, like Grafman and his colleagues (Gomez-Beldarrain et al. 2004), we emphasize the role of the PF cortex in dealing with distant time horizons. Tulving (2005) called this function mental time travel, and Chapter 9 explains the importance of imagining scenarios and engaging in mental trial-and-error behaviour.

Supervisory attentional system

As explained in the previous section, Wood and Grafman (2003) contrast their theory with processing theories such as attentional control. Norman and Shallice (1980) produced a theory that contrasted ‘willed’ with automatic action. By willed action they referred to the attentional control of actions. The situations requiring attentive behaviour include those in which the expected outcome fails to occur, for example because the context has changed. In a later paper, Shallice (1982) specifically proposed that this supervisory attentional system relied on the PF cortex.

In later studies, Stuss and Alexander (2007) studied a large group of patients with frontal lobe lesions. They compared the effects of medial, left lateral, and right lateral lesions and concluded that they performed independent but interrelated behavioural control processes. In collaboration with Shallice, they demonstrated that medial and ventral PF lesions produce different effects on performance of the Stroop task (Alexander et al. 2007), that medial and dorsal PF lesions have different effects on task switching (Shallice et al. 2007), and that medial PF lesions and right lateral PF lesions have different effects on sustained attention (Stuss et al. 2005). Stuss (2006) and Shallice and Cooper (2011) have suggested that these and other data point to functional specializations within the supervisory attention system.

Our proposal incorporates some aspects of these ideas. In Chapter 8, for example, we review evidence that the granular PF cortex becomes more engaged when people or monkeys engage in novel tasks or when the task situation has changed, and we pointed out that this engagement decreases as the task becomes automatic. Thus, our proposal incorporates the role of the PF cortex in the attentional control of behaviour.

However, other cortical areas also play a role in such control. Baddeley and Sala (1998) concluded that the ‘central executive’ can be regarded as a supervisory attentional system and that other areas, such as the posterior parietal cortex, also play a crucial role in these functions. If so, then the supervisory attention theory fails the specificity test. We accept, however, that the theory might, at some future time, be reformulated to make it specific to the PF cortex.

Furthermore, the patients in these studies have large lesions, and the attempt at localization depends on the relatively crude technique of plotting the overlap among lesions, without any serious assessment of the white-matter damage that could produce impairments very distant from the region of overlap. Chapter 1 explains that it is for this reason that we rely so heavily on the more selective, grey-matter lesions that can be made in studies of monkeys.

The supervisory-attention theory also fails to address the anatomy test because it does not give an account of how the connections allow the PF cortex to do what it does. It does

not address the history test. And, like other theories that invoke the concept of executive functions, the ideas are formulated so generally as to preclude falsification.

Multiple-demand system, global workspace, and general intelligence

We touched earlier upon aspects of the multiple-demand theory and general problem-solving in relation to research on monkeys. However, the main impetus for these ideas comes from research on humans. Dehaene et al. (1998), for example, has suggested the term *global workspace* to describe the function of the PF cortex. Their idea invokes the concept of domain generality, that is, being able to call on information from more specialized systems and integrate that information to make decisions and choices. Typically, the workspace is viewed as acting serially, such that it can only attend to one choice at a time.

The global workspace theory relates closely to the multiple demand theory as proposed by Duncan (2010b). In a meta-analysis of imaging studies, Duncan and Owen (2000) described activations in the dorsal PF cortex for a wide variety of tasks, including those that test perception, motor learning, and working memory. Activation occurred in much the same area when people engaged in fluid reasoning (Duncan et al. 2000). Putting the two sets of findings together, Duncan proposed that a large part of the PF cortex functions to support nearly any behaviour of a difficult or demanding nature.

These theories point to important functions of the PF cortex, such as problem solving and the ability of the PF cortex to integrate information across cognitive domains. Our proposal, like the global workspace and multiple demand theories, stresses the integration of information across sensory modalities and cognitive domains. We agree that the PF cortex has something to do with problem-solving in demanding situations, problem-solving across sensory and cognitive domains, and the attentive control of behaviour.

However, as formulated, these theories fail or fail to address several tests. They do not address the history test. They fail the specificity test because both the multiple demand system of Duncan and the global workspace theory of Dehaene et al. include the posterior parietal cortex as well as the prefrontal cortex. For example, Woolgar et al. (2010) have shown that both prefrontal and posterior parietal lesions impair the ability to engage in fluid reasoning. And imaging experiments often lead to the joint activation of the PF cortex, the posterior parietal cortex, and a part of the medial frontal cortex. Duncan (2010b), for example, defines his multiple demand system in just this way, so it fails the specificity test from the start.

These theories also seem to lack the precision required for refutation, and thus in their present version they probably fail the falsifiability test, and so we enter a query in Table 10.2 in the appropriate column.

Summary

Like the proposals based on monkey research, those based mainly on human research fail one or more of the five tests applied. None of these theories properly addresses the history test, and some could never do so. Furthermore, these theories often pay little attention to connectional anatomy and thereby fail the anatomy test. Some theories fail the specificity

test because they do not say what the PF cortex does that the posterior parietal cortex does not do. Other theories depend on just a few tasks, and so fail the generality test. And some of the theories could explain anything, and so they fail the falsifiability test.

Our proposal assessed against the same criteria

We have been critical when considering theories in the literature, and yet it will be obvious our proposal bears similarities with many of them. Indeed it would be odd if it did not, because theories depend on data, and theories of the PF cortex attempt to explain a similar range of data. However, we think that the alternative theories fail tests that our proposal can pass.

So now we evaluate our own proposal, and we do so in two ways. First, we consider how it fares when evaluated against the history, anatomy, specificity, and generality tests. Of course, we have devised our proposal with these criteria in mind, but we still need to explain how it meets them. Second, we advance various ways to refute our proposal, thus satisfying the falsifiability test.

History test

A comprehensive theory of the primate PF cortex must take evolution into account. Chapter 2 explains that much of the granular PF cortex first appeared in early primates and that additional PF areas evolved in anthropoid primates. We propose specific advantages that these new areas conferred on early primates and on anthropoid primates at a particular time and place in their evolutionary history (Chapters 2 and 8). We think that their new PF areas gave early primates a selective advantage in adapting to the fine-branch niche. The additional PF areas that anthropoids evolved enabled them to generate goals on the basis of single events, thereby reducing errors in foraging choices made during periods of dearth and attrition.

We stress that in developing these ideas, we have based our analysis on evidence rather than upon suppositions about how evolution ‘must have’ worked, as sometimes occurs in the existing literature. Of course, we need much more evidence, and we know that not all of the evidence that we have has the same level of reliability.

Anatomy test

Chapters 3–7 explain how the connections of the PF cortex determine what it can do, and Chapter 8 extends this idea to the PF cortex, as a whole. Take the orbital PF cortex, for example. Chapter 4 points out that its connections with olfactory, gustatory, visceral, somatosensory, and visual cortex, along with the amygdala, places it in a unique position to encode the specific sensory properties of the foods and fluids and assess their value in terms of up-to-the-minute biological needs. Similarly, Chapters 6 and 7 explain that the functions of the dorsal and ventral PF cortex depend, in part, on their connections with the posterior parietal cortex and the temporal cortex, respectively.

Specificity test

A successful theory must explain why the PF cortex can perform the proposed function, but other parts of the brain cannot. In each of the chapters on subdivisions of the PF

cortex (Chapters 3–7), we contrast the functions of the PF cortex with those of other areas, such as the posterior parietal, temporal, premotor, or hippocampal cortex. Chapter 8 extends this argument to the PF cortex as a whole. It is not enough, in our view, so say what the primate PF cortex does. In this book, we also say what it does that other brain areas cannot do.

Generality test

The generality test requires that a successful theory must account for the broad range of data available for the PF cortex and for the functions of all parts of the PF cortex. Tables 8.1, 8.2, and 9.1 compile lists of lesion effects, cell-activity properties, and imaging activations, respectively. As already mentioned, many of the theories in the literature depend on just one or a few tasks or focus on one or a few parts of the PF cortex. Our proposal accounts for a wider range of the tasks and cell types than many other proposals in the literature. It also accounts for all parts of the PF cortex. In this way, it passes the generality test.

Falsifiability of our proposal

It does not matter if a theory meets the other criteria if it fails to pass the falsifiability test. In suggesting tests of our proposal, we have in mind that they be practicable and not dependent on methodologies with little prospect for application in the near future, such as recording simultaneously from all of the neurons in the cortex or developing imaging methods that detect the activity of single cells.

In considering observations that would conflict with our proposal, we organize them by the history, anatomy, specificity, and generality tests. For the specificity test, we divide the discussion into tests that involve areas other than the PF cortex and those that involve species other than primates.

History test

Our theory emphasizes the evolutionary history of the PF cortex, and our views will undoubtedly raise some eyebrows among neuroscientists. Discussions of brain evolution can seem speculative to neuroscientists, even when based on sound evidence. Several factors contribute to this perception. First, we do not have all the evidence we want. This difficulty applies to everything in neuroscience, of course, but it seems more forbidding for events that occurred millions of years ago. Second, brains and axonal connections do not fossilize, so palaeontology offers less insight into the brain than it does for teeth and bones. Third, neuroscientists often harbour undue scepticism about the likelihood of convergent and parallel evolution. Could independent evolution leading to cats and monkeys have produced frontally directed eyes, retinal specializations something like the fovea, smooth-pursuit eye movements, and cortical areas something like the inferior temporal cortex? It seems unlikely to many neuroscientists, but it happened. Foveas, for example, have evolved independently many times in vertebrate history, including in certain lizards, early birds, and early haplorhine primates (Ross 2004).

So the finding of something that resembles the inferior temporal cortex and projects to something that someone calls the prefrontal cortex in dogs or cats or sheep, for example, does not pose a challenge to our ideas about the evolution of the PF cortex in primates. On the other hand, convincing evidence for homologues of the ventral or mid-lateral PF cortex in a nonprimate mammal would contradict our proposal.

Note that in considering such objections to our proposal, it is not enough to call an area prefrontal or, to cite another example, the frontal pole. The proposed homology must be supported by a constellation of properties that collectively identify the area and distinguish it from others. For reasons that Chapters 2, 3, and 4 all explain, it is not enough to point to similarities. These criteria must be diagnostic of a certain area. This standard is exacting, but it can be met if nonprimate mammals have a homologue of the granular PF cortex, in general, or specific areas such as the mid-lateral or polar PF cortex.

Stated more generally, any findings that seriously undermine our conclusions about the evolutionary history of the primate PF cortex would challenge our proposal because these conclusions serve as its foundation.

Anatomy test

A complete theory of the primate PF cortex should explain why its connections enable the proposed function. We have attempted such explanations in Chapters 3–8, but as we explain in Chapter 1, the accepted anatomy changes from time to time. This is as it should be. Neuroanatomists make mistakes because the methods that they use have limitations, often severe ones. This problem applies both to connectivity analysis and to the demarcations of cortical fields.

In Chapter 1, we point to the value of observer-independent cytoarchitectonic analysis. Someday, maps of that kind will be available for both monkeys and humans, and some reasonable initial steps have already appeared. An enhanced understanding of the subdivisions of the granular PF cortex could change the way we interpret the connections that we sketch as connectional fingerprints in Chapters 3–7. For example, when we say that a connection terminates in some area, our interpretation could be wrong. Those axons may terminate in a patch of cortex that we now consider to be part of one area, but observer-independent definitions may lead to its inclusion in some other area someday. These revisions could challenge our thesis, or at least cause substantial revision.

Minor changes in the anatomy would not seriously challenge our proposal. We expect such changes as new results become available or additional published anatomical results enter into the discussion. But major differences could undermine our proposal considerably. For example, if future research shows that the PF cortex has few outputs to the premotor cortex, it would present difficulties in understanding how the cortex transforms goals into the targets of action. Attitudes about the functional significance, extent, and organization of connections from the PF to the premotor cortex have waxed and waned over the decades. The prevailing view may, in the future, change yet again. Likewise, if future neuroanatomists conclude that the posterior parietal projections to the granular PF cortex arise from a restricted part of the parietal lobe that lacks the properties for the

processing of time, order, and spatial information, one could reject our explanation of how the dorsal PF cortex does what it does.

The anatomy test requires us to say how its connections allow the PF cortex to perform its function. If an experiment produced evidence that disconnecting the various parts of the PF cortex from each other left its key function intact, our proposal would fail. The idea that event-related inputs from the hippocampus, for example, affect goal-generation in the mid-lateral, ventral, dorsal, and polar PF cortex assumes that they do so through intrinsic PF connections, at least in part (Chapter 8). If an experimental procedure blocked these intrinsic connections, and the advanced behaviours continued unabated, our proposal could not cover such results. Inactivation or disconnection of all the PF targets of the hippocampus would, presumably, block the requisite relays. We do not mean to single out the hippocampal inputs in particular, although they seem especially interesting; a similar approach could test the other sources of context information, such as those emanating from the posterior parietal, temporal, or olfactory cortex.

Specificity test: other areas

Our proposal would fail if evidence comes to light that some other part of the brain does what we say the PF cortex does, especially if it has relatively direct access to premotor areas.

Ideas about access to the premotor areas change from time to time. The traditional view of the basal ganglia, for example, considered it to be the site of convergence of sensory information from many cortical areas, such as the inferior temporal cortex, with outputs to the premotor and primary motor cortex via the thalamus. In the past, neuro-anatomists saw the basal ganglia as a route from the inferior temporal cortex and the PF cortex to the premotor areas (Kemp & Powell 1971). As we explain in Chapter 8, this view has gone out of fashion because of the work of Strick and his colleagues (Middleton & Strick 2000), who emphasize parallel cortex–basal ganglia loops, with only some of these loops having access to the premotor and primary motor cortex. But the traditional ideas might experience a rebirth or re-emphasis in the future, and if they did we would have to revise certain aspects of our proposal.

Other parts of the cerebral cortex cooperate closely with the granular PF cortex, including the posterior parietal cortex. We view the posterior parietal cortex as supplying context information to the granular PF cortex, as Chapter 6 explains. But if some part of the posterior parietal cortex is found to generate goals based on that context, using nonspatial as well as spatial contexts and information about specific outcomes, these findings would contradict our proposal. At the moment, we do not think that the available data refutes our proposal, but future results might.

We mentioned earlier that the hippocampus also has many of the properties of the granular PF cortex. Cell activity changes in the hippocampus during conditional visuo-motor mappings (Cahusac et al. 1993; Yanike et al. 2009), much as it does in the granular PF cortex (Pasupathy & Miller 2005). If future research shows that the hippocampus performs the function that we ascribe to the granular PF cortex, our proposal would fail.

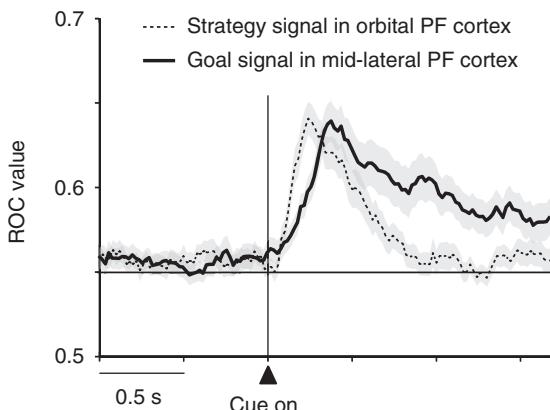


Fig. 10.2 Relative time course of neural signals in two cortical areas. The receiver operating characteristic (ROC value) quantifies the ability to decode the signal on a trial-by-trial basis. The strategy signal in the orbital PF cortex (dashed line) preceded the goal signal that developed in the mid-lateral PF cortex (solid line). Shading: SEM. Modified from Tsujimoto S, Genovesio A, Wise SP. Comparison of strategy signals in the dorsolateral and orbital prefrontal cortex. *Journal of Neuroscience* 31:4583–92, © Society for Neuroscience, 2011, with permission.

Further studies could also compare the timing of the signals that are pertinent to our proposal, especially those reflecting the generation of goals. Figure 10.2 shows that a strategy signal develops in the orbital PF cortex before the signal encoding the current goal develops in the mid-lateral PF cortex (Tsujimoto et al. 2011a). This example compares two PF areas, but the same approach could compare the timing of signals in any two areas. If goal signals develop earlier in areas other than the PF cortex during attentively controlled goal generation, this would count as evidence against our proposal.

At first glance, such data appear to be available already. Wallis and Miller (2003a) compared the latencies of rule-encoding signals in the PF cortex and the dorsal premotor cortex. These cells encoded the matching- and nonmatching-to-sample rules as we explain in Chapter 7. The rule signal developed in the premotor cortex before it appeared in the PF cortex. This finding would seem to pose a challenge to the idea that the PF cortex generates goals. As Chapter 8 explains, however, the proposal about goal generation applies only to attentive control. When monkeys and people control their behaviour automatically, the PF cortex becomes relatively disengaged. The results on this task have relied on rules that the monkeys had overlearned to the point of automaticity (Wallis & Miller 2003a; Muhammed et al. 2006). No one has studied the relative timing of neuronal activity in the PF and premotor cortex during the *learning* of abstract behaviour-guiding rules or strategies.

Specificity test: other species

If we are right that the granular PF cortex evolved in primates after their divergence from other mammalian lineages (Chapter 2), then a theory of the PF cortex cannot depend exclusively on data from nonprimate mammals. Nevertheless, a current view of the PF

cortex in rodents holds that it consists either of an amalgam of all of the PF areas in primates, granular and agranular, or a miniaturized version of the primate PF cortex. On either view, the function of the rodent PF cortex is held to be more-or-less the same as that of the primate PF cortex. If this view is correct, then our proposal is wrong. It would fail the specificity test because functions that we attribute to primate-specific areas can instead be performed by other parts of the brain. If they can do so in other animals, the homologous areas might have the same capacity in primates. At the least, such findings would shift the burden of ‘proof’ more toward our side.

We address this issue briefly and separately for the medial PF cortex in Chapter 3 and for the orbital PF cortex in Chapter 4. Chapter 2 deals with many of the general issues, with only brief mention of the behavioural evidence. Here we address the behavioural evidence in more detail.

On their own, the behavioural data from rats alone tell us nothing about anthropoid primates. Adding observations from mice adds little more because these closely related muroid rodents have diverged so recently. Convergent and parallel evolution is common, and the rodent and primate lineages split ~70–90 Ma (see Figure 2.8). Modern rodents and primates have therefore evolved separately for a long time, and during this time they have adapted to the problems and opportunities that they have encountered. In many instances, they might have encountered similar problems or opportunities, and they might have solved or exploited them in a similar way.

Behavioural evidence from rodents could become relevant to primates, however, if added to evidence from an appropriate selection of mammals. Figure 2.8 shows how one might choose a sufficient diversity of mammals to study. We have placed a hashtag (#) above lineages that, collectively, should tell us about the common ancestor of many mammals. Without reference to a last common ancestor, similarities among modern mammals have little probative value.

To make this suggestion concrete, we point to four groups of mammals for future study: tenrecs, moles, rabbits, and hedgehogs. One could choose species in other groups, of course, but these mammals will do for the sake of discussion. Combined with information from rodents and primates, traits common to most or all of these species should reflect those of their last common ancestor, also marked by a hashtag (#) in Figure 2.8. All of those species are small animals that could be tested in a standard psychology laboratory with feasible modifications. All have been studied by neuroanatomists, and two are household pets. The barriers to studying these creatures are conceptual, not pragmatic.

The ability of all or most of these species to perform the behaviours that we attribute to the granular PF cortex of anthropoid primates—at the same level—would be evidence that these traits evolved in early mammals. If that is the case, then our proposal must be wrong.

Despite the principle that a comparison of just two extant species tells us almost nothing, we realize that many readers will be interested in the comparison of rats and monkeys. We begin our discussion of that topic by considering the delayed response task and

other tests said to assess spatial memory. In comparing rats and monkeys on these tasks, we need to distinguish three questions clearly:

1. Given that rats lack a granular PF cortex, can they perform tasks that depend on the granular PF cortex in monkeys?
2. For tasks that depend upon the granular PF cortex in monkeys, do significant impairments follow lesions of the rat agranular PF cortex?
3. When the answer to question two is affirmative, do these impairments have the same character after lesions in rats and monkeys?

Chapter 6 explains that the dorsal PF cortex, and in particular its mid-lateral component (area 46), is essential for correct performance of the delayed response and delayed alternation tasks in monkeys. Monkeys with no training before removal of the mid-lateral PF cortex fail to learn the delayed response task at all, even after 500 trials with a brief, 1-second interval (Battig et al. 1960). Monkeys with large dorsal PF cortex lesions also fail to learn the delayed alternation task after 4000 trials (Goldman & Galkin 1978). When the monkeys have learned the task rules prior to the lesion, bilateral PF cortex lesions cause performance to drop to chance level on the delayed response task, and remain there indefinitely. With a 5-second delay interval, some monkeys perform at chance level for 1000 trials, at which point the experimenters usually stop testing them (Mishkin 1957; Goldman et al. 1971). When trained with a 4-second interval, monkeys remain at chance levels even when tested with easier, 2-second intervals (Kojima et al. 1982). So there can be no doubt that, in monkeys, the performance of these tasks requires the mid-lateral PF cortex, which is a granular area.

In this context, it strikes some neuroscientists as significant that rats can learn spatial memory tasks of this sort. This finding answers question one. Rats can learn working memory tasks, such as the 8-choice radial arm-maze task (Olton et al. 1982; Kesner 1989), the delayed response task (Kolb et al. 1974), and the delayed alternation task (Thomas & Brito 1980; Bannerman et al. 2001). They can also learn the delayed matching-to-position and the delayed nonmatching-to-position tasks, and can do so whether tested in an operant chamber (Sloan et al. 2006) or a T-maze (Dias & Aggleton 2000).

The ability of rats to perform these tasks should come as no surprise because they are simple compared to many of the tasks that monkeys can perform. Furthermore, as Chapters 5 and 6 explain, these tasks do not test specific cognitive processes and so they can be solved in many different ways.

Question two deals with lesion effects in rats. Chapter 3 explains the opinion of some neuroscientists that the medial PF cortex in rats, an agranular area, is homologous to the mid-lateral PF cortex in monkeys and humans, a granular area. And in support of this idea, Kolb et al. (1974) found that lesions of the rat medial PF cortex caused a significant deficit on the delayed response task. There are other results of this kind. We do not dispute the significance or the severity of these lesion effects. But as we explain in Chapter 3, these findings say nothing about homologies because significant impairments on these tasks also follow lesions of the agranular PF cortex, including the anterior cingulate cortex

and the prelimbic cortex, in monkeys (Meunier et al. 1997; Rushworth et al. 2003). So if one simply asks whether a lesion of the medial PF cortex causes a significant impairment on the delayed response task in rats, the answer is that it does. But this result does not provide a suitable diagnostic criterion for identifying homologies.

Question three goes beyond a simple classification of post-lesion behaviour as either impaired or normal performance. Examination of the details of lesion effects in rats and monkeys suggests that rats and monkeys do not solve the problems in the same way. First, in experiments on the delayed response task (Kolb et al. 1974), radial arm maze (Kesner 1989), and matching- or nonmatching-to-position in an operant chamber (Sloan et al. 2006), nothing is done to prevent the rats from bridging the delay by orienting to the correct side or approaching it. Second, if the animals are tested on delayed alternation in a T-maze, and thus cannot solve the problem through an orientation strategy, the trials are very widely spaced and the animals can solve the problem on the basis of familiarity or recency (Sanderson et al. 2010).

Rats also have ways of navigating to locations on the basis of memory (Kolb et al. 1994), and the connections between the medial PF cortex and the hippocampus mediate this function in some spatial tasks. Lesions of these structures cause impairments on tasks in which the rats must navigate in spatial fields, such as the Morris water-maze task and the radial arm maze task (Kolb et al. 1994). Transection of the fornix causes an impairment in the delayed nonmatching-to-sample task, as tested in a T-maze (Markowska et al. 1989), and the same result occurs in macaque monkeys tested in the same way (Murray et al. 1989). So the impairment on these tasks could reflect damage to a navigational system, which in monkeys operates in parallel with a reaching system. We note, however, that rats with lesions of the hippocampus and surrounding areas perform normally on the delayed response task, unless the delays exceed 30 seconds (Alvarez et al. 1994). So for this particular task, an account in terms of navigation seems unlikely.

As significant as they are, the impairments that follow medial PF cortex lesions in rats are not nearly as severe as the impairments on the delayed response and delayed alternation tasks in monkeys with mid-lateral PF cortex lesions. After medial PF lesions, rats trained on the delayed response task can reach 90% correct performance at a median interval of 2 seconds in just 140 trials (Kolb et al. 1994). In another test of spatial memory, rats with similar lesions showed a mild impairment initially but regained a normal level of performance in just 60 trials (Kolb et al. 1974). The investigators needed to use a titration procedure to demonstrate a lesion effect precisely because the lesioned rats successfully solved the problem at short delays (Kolb et al. 1994); monkeys with lesions of the mid-lateral PF cortex could never do that.

On the basis of what we have said so far, we can reject the idea that the medial PF cortex is homologous with the mid-lateral PF cortex (area 46) in primates, or with any other granular PF area. Accepting this conclusion, Brown and Bowman (2002) attempted to make the case for analogy, as opposed to homology. On this view, the medial PF cortex of rodents and the granular PF cortex of primates both play a role in spatial working memory, and so they have the ‘same’ function. However, in Chapter 6 and again in this chapter we explain the inadequacy of the working memory theory for the primate PF cortex, in

general, or for the mid-lateral PF cortex (area 46), in particular. The key problem with the argument for analogy is that it fails to distinguish among the many different kinds of spatial analysis that animals engage in. Monkeys, for example, navigate through space, reach for and manipulate objects in a spatial frame of reference, judge relative distances on both fine and coarse scales, and discriminate one place from another. Spatial information can be computed in terms of an intrinsic frame of reference or an extrinsic one, often termed egocentric and allocentric, respectively. The behavioural tasks devised to date do not differentiate these factors with sufficient precision to make a case for the analogy of medial PF cortex with any granular part of the PF cortex in primates.

The critical question, therefore, is whether rats and monkeys solve the delayed response task in the same way. Chapter 6 explains how we think that monkeys solve the delayed response task, and that account appeals to the concepts of interference, rules, and prospective coding. By prospective coding we refer to maintaining a goal in memory when the goal is not visible, as, for example, during the delay period of the delayed response task. Our account holds that monkeys perform the delayed response task by using a rule (that the location of the most recent visual event tells them what to do next) and prospectively encoding that goal in order to defeat interference from previous events, including previous cues and goal choices. We would consider evidence that rats do the delayed response task in precisely this way, if it could be produced, to be of considerable interest. It would be yet more interesting if evidence came forward that lesions of some part of the rat frontal cortex caused an impairment as severe as the one caused by lesions of the mid-lateral PF cortex in monkeys. And if similar results appeared in a diverse selection of mammals, along the lines explained earlier, that would show that our proposal is wrong.

Readers might still wonder why, when monkeys also have most of their brain intact after mid-lateral PF cortex lesion, they cannot solve the simple problem posed by the delayed response task. Chapter 6 gives the reason, which the previous paragraph restates. To put the same idea in other words, the lesioned monkeys either: (1) cannot sort out the order past visual events, (2) cannot remember or use the rule that the most recent event guides the current choice, or (3) cannot use prospective coding to overcome the interference that comes from the memory of previous trials.

Because of their unique evolutionary history, anthropoid primates solve the problem posed by the delayed response task in this way. Accordingly, normal monkeys have no need to resort to orientation strategies—and so perhaps for this reason lesioned monkeys do not do so either. Furthermore, because normal monkeys depend on reaching in a fixation-centred frame of reference (Chapters 2 and 5), they depend on their mid-lateral PF cortex to provide the premotor areas with a goal in that coordinate frame, especially for invisible targets. (For visible targets, the posterior parietal and premotor areas suffice.) It might seem counterintuitive to say that anthropoids use a visual frame of reference to reach for invisible targets, but the evidence adduced by Shadmehr and Wise (2005), as briefly summarized in Chapter 2, shows that this is indeed the case.

So far, we have addressed this issue through the lens of the delayed response tasks and related tests of spatial information processing. But the functions of the granular PF cortex extend well beyond those assessed by the delayed response task. In Chapter 8, we propose

a more general set of advantages conferred by the primate PF cortex: fast learning, the ability to reduce errors by applying abstract rules and strategies, and the ability to link choices to outcomes based on single events.

Note that none of these advantages have an all-or-nothing nature. We do not claim that other mammals cannot learn quickly under some specialized circumstances (analogous to the taste aversion effect or imprinting in chicks). We do not believe that the use of abstract rules and strategies *per se* is confined to primates. And for choice–outcome or stimulus–outcome associations, we say only that primates evolved two key advances, involving the predominance of vision and the assignment of credit based on single events. Other mammals see, other mammals learn stimulus–outcome associations, other mammals learn quickly, and other mammals use abstract strategies. We claim only that during their evolution anthropoid primates came to make foraging choices better and faster, with fewer errors than their ancestors, because of advances in these abilities. Natural selection requires an advantage, not a completely new capacity. There is no magical difference between one-trial learning and ten-trial learning, just the extra errors in the latter instance. And the same capacity can be achieved by different means through parallel evolution. Thus our argument does not require that we say what specific task a monkey (or some other primate) can do that a rat (or some other mammal) cannot do.

Nevertheless, we find it interesting that primates have mastered some tasks that no rodent ever has. No rat has ever learned the strategy task that Genovesio et al. (2005) reported for monkeys (Chapter 7). To our knowledge, no one has ever attempted to train a rat to perform that task, but we would find it remarkable if someone could do so.

Although we do not consider it necessary, it is heuristically useful to consider tasks that might fall beyond a rodent's reach. To be fair about such a comparison, we should propose a task that no one has yet taught either a rat or a monkey to do. So we predict that monkeys, but not rats, can master the following task: having learned the 'repeat-stay' and 'change-shift' strategy task of Genovesio et al. (2005), the subjects must now learn to reverse these strategies and develop 'repeat-shift' and 'change-stay' strategies instead, and to reverse repeatedly as in reversal set experiments (Chapter 4). The ability to do this would reflect a learning capacity that we suspect requires the granular PF cortex.

In another task, the subjects would later need to learn to use a cue to switch between these two sets of strategies: 'repeat-stay' and 'change-shift' in response to one cue; 'repeat-shift' and 'change-stay' in response to another cue. The most tractable version of this task would use blocks of about five trials or so because the strategies deal with information carried across trials.

A third such task might involve combinations of behaviours that depend on the granular PF cortex in monkeys. For example, subjects would first develop a strong learning set on the conditional visuomotor task, as Chapter 7 explains. For three novel stimuli, each one would instruct the subjects as to which of three actions would produce a reward. We know that monkeys can learn these mappings in just a few trials. Subjects would next learn the object-in-place scenes task to proficiency, which Chapters 3 and 8 explain. Unlike the standard version of the task, each scene would contain three potential choices. The rat version of the task could use tones for the background and odours as choices.

After this training, the subjects would need to combine the two tasks. They would have to learn both which object (or odour) to choose, based on the background stimulus (context), and the separate action associated with that object (or odour), based on trial-and-error learning. They would only have 20 trials per problem to learn these relationships, at which point a new set of stimuli and backgrounds would be presented. We predict that monkeys could learn such a task, but rats probably could not.

Of course, any failure to learn a particular task could simply reflect an inadequacy of the training methods or insufficient time for the subject to learn. For example, macaque monkeys can learn the reversed reward contingency task, in which they must learn to choose the lesser of two quantities of food in order to obtain the greater quantity (Murray et al. 2005). Yet a report by Silberberg and Fujita (1996) said that monkeys could not solve this problem. Silberberg and Fujita failed to teach their animals this task for a simple reason: they did not allow their monkeys enough trials. With more experience on the same task, monkeys can learn this task very well, indeed. But it took six monkeys a mean of 1087 trials to learn, and Silberberg and Fujita permitted their subjects only a fraction of that experience.

Notwithstanding the arguments made here, we expect that many neuroscientists will feel that our proposal is weakened by the observation that some other mammal learns the same thing as monkeys can and does so as efficiently. Dogs, for example, have a fast mapping ability for sounds that resembles the way humans learn word meanings (Kaminski et al. 2004). As we explain earlier, our proposal could accommodate a limited number of examples of such parallel or convergent evolution in a few species. But only so many.

Discrimination learning set provides an example that is already in the literature. We explain in Chapter 8 that the monkeys perform at nearly 90% correct on trial two and that a strong learning set depends on interactions between the inferior temporal cortex and the PF cortex. We placed this finding in the context of others in which monkeys can use single events to reduce errors. So our position would be challenged if rats can develop a discrimination learning set as fast and to the same degree as monkeys.

A paper by Slotnick et al. (2000) makes such a claim, but it is unconvincing for two reasons. First, they used a go no-go task. For each problem, the rats poked their nose into a chamber to sniff an odour. The experimenters designated one odour as a ‘go’ stimulus, another as a ‘no-go’ stimulus. This task has a serious flaw: a ‘go bias’. Because the costs of ‘going’ are so small, it pays animals to go by default, and then they get to the next trial faster. And, indeed, Slotnik et al. report that every error their rats made was an error of commission, that is, erroneous ‘go’ responses to ‘no-go’ stimuli. As a result, the experimental design renders the ‘go’ stimulus virtually irrelevant to the subjects, and this design flaw means that the tasks tests extinction learning and not discrimination learning.

Second, and perhaps more important, Slotnik et al. set up their experiment so that the odour came from the same place that the rats poked their nose, and the reward also occurred at that location. As a result, the experiment established perfect spatial contiguity among the stimulus, the response, and the reward. Spatial contiguity of this kind is known to promote very rapid learning (Cowey & Weiskrantz 1968), and indeed the rats studied by Slotnik et al. performed at a high level from the beginning of training. As a

result, their rats did not have to develop a discrimination learning set to perform the task well. When the location of the reward is separate from the location of the response, then rats learn a series of olfactory discriminations much more slowly (Fagan et al. 1985). Accordingly, the results of Slotnik et al. provide no evidence for the kind of discrimination learning set that macaque monkeys can attain (see Figure 8.2).

Another paper, by Eichenbaum et al. (1986), has been cited as demonstrating discrimination learning set in rats, but it says nothing about performance on the key trial, trial two.

The conditions for testing rats on learning set therefore have differed dramatically from those used for monkeys. A proper test of learning set in rats would require the choice between two non food stimuli, which leads to the later presentation of a reward in a different place, as in learning set experiments in monkeys. Visual stimuli should be perfectly adequate to test this ability, and Figure 8.2 shows that rats gain a learning set only weakly and slowly. There is a general sense in this literature that it is somehow unfair to require rats to choose among visual stimuli, but they have no trouble doing so in many other tasks, provided experimenters select the stimuli carefully (Bussey et al. 2008). Furthermore, squirrels have much better vision than rats, and they also develop a learning set slowly (see Figure 8.2). Nevertheless, if future studies show nearly 90% correct performance on trial two in a rat, in conditions comparable to those used in monkey experiments, it would count against our proposal. If replicated in a diverse sampling of mammals, it would show that our proposal is probably wrong.

The same goes for the one-trial learning of visuomotor mappings. Monkeys and rats (Dunn et al. 2005; Dumont et al. 2007) can both learn conditional visuomotor tasks. Fast learning of new mappings requires the granular PF cortex (Chapter 7), but slow learning does not (Bussey et al. 2001). If it could be shown that rats can learn novel conditional motor mappings in one or a few trials, as monkeys can, and that frontal lesions block one-trial learning, as they do in monkeys, the results would challenge our conclusions. If these finding were confirmed in a diverse selection of mammals, it would count as evidence against our proposal.

Finally, a word of caution. In Chapters 3 and 4, we advance ideas about the functions of the agranular PF cortex. We said that these areas are homologous in rats and monkeys (see Figure 2.1). This contention does not imply, however, that every connection, every cell-activity property, every imaging activation, and every lesion effect will be identical in rats and monkeys. Each lineage has been evolving separately for ~70–90 million years and quite a few changes have probably accrued over that long interval. In particular, when new granular areas evolved in the primate PF cortex, this probably caused significant changes in the older areas. If this caveat seems unfair, it is not our fault; it is just the way that evolution works.

Generality test

The generality test requires our proposal to account for the diverse data on the PF cortex, and for all of its parts. In our discussions of the medial PF cortex, however, we do not say very much about areas 9 and 10 because little experimental work has been reported for

these areas, especially in monkeys. We also cite few results for the agranular PF areas in monkeys. We cannot do anything about a lack of data, but this must nevertheless be counted as a weakness of our proposal.

We believe that our proposal accounts for the published literature reasonably well, but if a critic could point to some important finding that our proposal fails to explain, it would lead, at a minimum, to a reformulation. Likewise, if critics can point to some part of the PF cortex that our proposal fails to cover, putting aside a lack of evidence, that would count against us, too.

Conclusion

This book presents a new theory of the primate prefrontal cortex, but we do not claim our proposal lacks any precedents. It has many. For example, according to Fulton (1949), the nineteenth century neurologist Flourens ‘attributed to the frontal lobes, acting in harmony with the rest of the brain, the higher perceptual, associative and executive functions of the mind’ on the basis of lesion studies in hens. But this early proposal exemplifies the problems with many current theories of the primate prefrontal cortex: (1) it does not distinguish primates from other animals; (2) it does not say in what way the frontal lobes differ from other areas; and (3) it is so vague as to preclude falsification. So have we done better?

Taking the last point first, this chapter proposes some ways to test our theory. We have attempted to be sufficiently precise that critics can demonstrate the error of our ways. We are well aware that critics will claim—simultaneously in some cases—that our proposal is both wrong and already well known. Fine. Show how we are wrong and who had previously solved the riddle of the prefrontal cortex. The field will advance in either case.

As for the second point, Chapters 3–8 attempt to explain how the PF cortex differs from other parts of the brain, as well as how its connections account for its unique functions.

On the first point, we have made an extensive effort to distinguish primates from other mammals. Chapter 2 argues that certain granular PF areas evolved in early primates, with others appearing later, in anthropoid primates. In both cases, we propose that new PF areas appeared as primates adapted to a new kind of foraging. Chapter 2 also suggests that the agranular PF areas evolved in early mammals. Table 10.3 summarizes these ideas in the context of the functions proposed for major parts of the PF cortex.

Early primates restricted themselves to the fine branches of trees, and we propose that their new PF areas assessed the value of food items and searched for them in that cluttered environment. The caudal PF cortex contributed to search through top-down attention (Chapter 5). The orbital PF cortex enabled early primates to learn the value of choosing an object based on a single experience (Chapter 4).

Later, in the lineage leading to modern anthropoids, the fovea and trichromatic vision evolved and the brain expanded. During this expansion, new granular PF areas appeared, including the dorsal and ventral PF cortex, and probably the polar PF cortex, as well. The early anthropoids were small, but later ones became larger and expanded their foraging range. These animals moved along the larger branches of trees in the tropical rainforest,

Table 10.3 Evolution of the PF cortex in relation to niches and functions

Innovator	Niche	Function	Area
Early mammals	Nocturnal	Generates bias among competing actions	Agranular medial PF
		Generates bias among competing stimuli	Agranular orbital PF
Early primates	Nocturnal, fine-branch	Orients attention to visual stimuli of learned value	Caudal PF
		Learns and updates the value of visual stimuli	Granular orbital PF
		Generates goals based on visual and acoustic signs ^b of foods and fluids	Ventral PF
Advanced ^a anthropoids	Diurnal, large-branch (later terrestrial)	Generates goals based on the order, location, and timing of visual events	Dorsal PF
		Generates goals from 'internal' signals, including event memories	Granular medial PF

^a Advanced: importantly different from the early anthropoids.

^b Signs: conjunctions of sensory features at a hierarchical level between elemental features and whole objects.

foraged in daylight, moved long distances in search of food, risked predation to do so, and competed with birds and other primates. They needed an edge, and we propose that their new PF areas provided one. By using single events to generate foraging goals (Chapter 8), anthropoids could make fewer errors than their ancestors did. Errors are costly, errors are dangerous, and errors can be fatal. As anthropoids came to depend on rich—but volatile and dispersed—resources (Chapter 2), the ability to learn efficiently from single events likely paid a big dividend, especially in periods of dearth and attrition.

We have also proposed that the granular PF cortex evolved to augment the ancestral reinforcement-learning mechanism (Chapter 8). This older learning system adjusts behaviour slowly, based on accumulated experiences averaged over many events. It inevitably leads to a large number of errors when circumstances change. The ability to reduce the errors, along with their associated costs and risks, must provide a crucial advantage, and we think that the granular PF cortex delivers that advantage to primates.

As a result, compared to other mammals and compared to the ancestors of primates, anthropoid primates can better anticipate what they should do and what will happen; they can master advantageous behaviours faster and over a broader range of time horizons; they can learn the contexts for specific actions through more diverse combinations of inputs; they can behave more flexibly; they can maintain goals in memory while remaining flexible about the means for achieving them; they can more effectively ward off interference in memory; they can learn about abstractions and categories of behavioural contexts; and they can generate goals based on abstract rules and strategies. All of these capacities reduce errors.

Our proposal does not imply that other animals have nothing like these advantages. We claim only that an ability to use single events to choose goals, learn faster, and assign

causal responsibility to outcomes provided an edge at an important period in the history of our ancestors.

General-purpose learning and the origin of insight

The idea that the primate PF cortex performs some kind of global, cross-domain function has attracted considerable attention (Dehaene et al. 1998; Gaffan 2002; Duncan 2010b). As an earlier part of this chapter says, there is merit enough in that idea. But we think that it follows from something more fundamental. We think that the primate PF cortex evolved to solve specific ecological problems, first in early primates and later in anthropoids. Primates solved their *specific* problem, however, by developing a new general-purpose learning system, one that overcame the sluggishness of the ancestral general-purpose learning system. As a result, we think that our proposal says something important to both traditional cognitive psychology and evolutionary psychology.

In Chapter 9, we suggest that the fundamental function of the anthropoid PF cortex established the foundation for human insight. Through the power of re-representation, early modern humans evolved the ability to engage in mental trial-and-error behaviour. Because they could re-represent their own intentions, they could represent the intentions of others. They could imitate the actions of others because they could represent not only what a member of their social group did, but also his or her intended goals. And because they could represent the mental states of others, they could influence them by instruction. Re-representation allows humans to extend the advantage provided by the anthropoid PF cortex—a reduction in errors—to the elimination of errors entirely, at least in principle.

In the epigraph of this book, Russell refers to Köhler's intuitions about insight in animals. No one knows whether animals have insight in the sense that Köhler implied, but people surely do. We have used what insight we might have to generate a new theory of the prefrontal cortex. We could do so because new prefrontal areas evolved to help early primates find and evaluate resources in the fine-branch niche (Chapter 2); we could do so because additional prefrontal areas evolved to help anthropoid primates reduce foraging errors (Chapters 2 and 8); and we could do so because our human ancestors elaborated these mechanisms to further reduce errors—and possibly avoid them altogether—through instruction, imitation, and mental trial-and-error (Chapter 9). That is why we subtitled this book 'the origin of insight'. We have tried, but it is up to readers to decide if our account is in error.

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