Emotion Explained

Edmund T. Rolls
University of Oxford
Department of Experimental Psychology
Oxford
England

OXFORD UNIVERSITY PRESS • OXFORD 2005

Preface

What produces emotions? Why do we have emotions? How do we have emotions? Why do emotional states feel like something? This book seeks explanations of emotion by considering these questions.

One of the distinctive properties of this book is that it develops a conceptual and evolutionary approach (see for example Chapters 2 and 3) to emotion. This approach shows how cognitive states can produce and modulate emotion, and in turn how emotional states can influence cognition. Another distinctive property is that this book links these approaches to studies on the brain, at the level of neuronal neurophysiology, which provides much of the primary data about how the brain operates; but also to neuropsychological studies of patients with brain damage; to functional magnetic resonance imaging (fMRI) (and other neuroimaging) approaches; and to computational neuroscience approaches. The author performs research in all these areas, and this may help the approach to emotion described here to span many levels of investigation. The empirical evidence that is brought to bear is largely from non-human primates and from humans, because of the considerable similarity of their visual and emotional systems associated with the great development of the prefrontal cortex and temporal lobes in primates, and because the overall aim is to understand how emotion is implemented in the human brain, and the disorders that arise after brain damage.

To understand how the brain works, including how it functions in emotion, it is necessary to combine different approaches, including neural computation. Neurophysiology at the single neuron level is needed because this is the level at which information is exchanged between the computing elements of the brain. Evidence from the effects of brain damage, including that available from neuropsychology, is needed to help understand what different parts of the system do, and indeed what each part is necessary for. Neuroimaging is useful to indicate where in the human brain different processes take place, and to show which functions can be dissociated from each other. Knowledge of the biophysical and synaptic properties of neurons is essential to understand how the computing elements of the brain work, and therefore what the building blocks of biologically realistic computational models should be. Knowledge of the anatomical and functional architecture of the cortex is needed to show what types of neuronal network actually perform the computation. And finally the approach of neural computation is needed, as this is required to link together all the empirical evidence to produce an understanding of how the system actually works. This book utilizes evidence from all these disciplines to develop an understanding of how emotion is implemented by processing in the brain.

The overall plan of the book is as follows. Chapter 1 outlines the ways in which this book approaches different types of explanation of emotion, and introduces some of the concepts. Chapter 2 then considers the nature of emotion, producing a theory of emotion, and comparing it to some other theories. Chapter 3 considers the functions of emotion, and leads to a Darwinian theory of the adaptive value of emotion, which helps to illuminate many aspects of brain design and behaviour. Chapter 4 takes the explanation of emotion to the level of how emotion is implemented in the brain. Chapters 5 and 6 extend and complement this

by extending the approach to motivated behaviour in which affect is an important component. In Chapter 5 the motivated behaviour considered is hunger, and in Chapter 6 thirst. Chapter 7 extends the approach to reward and affect produced by brain stimulation, and Chapter 8 to the pharmacology of emotion and addiction. Chapter 9 extends the approach further, to sexual behaviour. Chapter 10 then considers the issue of emotional feelings, which is part of the much larger issue of consciousness. Chapter 11 then synthesizes some of the points made, including how decisions are made and are influenced by emotions. Appendix 1 describes some of the computational framework for understanding how systems in the brain in the form of neural networks perform emotion-related learning. Appendix 2 describes an example of a more detailed neural network approach to emotion-related learning in which the analysis extends from the level of the spiking activity of single neurons up through many levels of investigation to global properties of the system such as the signals measured in functional neuroimaging investigations, and the resulting behaviour. Appendix 3 provides a Glossary of some of the terms. The book thus seeks to explain emotions in terms of the following: What produces emotions? Why do we have emotions? How do we have emotions? Why do emotional states feel like something?

This book evolved from my earlier book *The Brain and Emotion* (Rolls 1999a) in some of the following ways:

Emotion Explained goes beyond brain mechanisms of emotion, in that it seeks to explain emotions in terms of the following: What produces emotions? (The general answer I propose is reinforcing stimuli, that is rewards and punishers, but with other factors too.) Why do we have emotions? (The overall answer I propose is that emotions are evolutionarily adaptive as they provide an efficient way for genes to influence our behaviour to increase their success.) How do we have emotions? (I answer this by describing what is known about the brain mechanisms of emotion.) Why do emotional states feel like something? This is part of the large problem of consciousness, which I address in Chapter 10. It is in this sense that a broad-ranging explanation of emotion going beyond the brain mechanisms of emotion is the theme of this book.

Emotion Explained goes beyond the brain mechanisms of emotion by developing my approach and theory of the nature of emotion, and comparing my approach to a range of different approaches to the nature of emotion, including the approaches of A.Damasio, J.LeDoux, J.Panksepp, and appraisal theorists such as K.Scherer.

Another way in which this book goes beyond brain mechanisms of emotion is to propose in Chapter 3 a Darwinian account of why animals (including humans) have emotions. The theory will I believe stand the test of time, in the same way as Darwin's theory of evolution by natural selection, and argues that emotions have the important evolutionary role of enabling genes to specify the goals (i.e. the rewards etc that produce emotions) for actions, rather than the actions themselves. The advantage of this Darwinian design is that although the genes specify the goals, the actual actions are not prespecified by the genes, so that there is great flexibility of the actions themselves. This provides a new approach to the nature vs nurture debate in animal behaviour, for it shows how genes can influence behaviour without specifying a fixed, instinctive, behavioural response. I hope that this will make the book of interest to a wide audience, including many interested in evolution and evolutionary biology.

Although in evolution Darwinian processes lead to gene-defined goals, it is also the case that in humans goals may be influenced by other processes, including cultural processes. Indeed, some goals are defined within a culture, for example writing a novel like one by

Tolstoy vs one by Virginia Woolf. But it is argued that it is primary reinforcers specified by genes of the general type shown in Table 2.1 on page 18 that make us want to be recognised in society because of the advantages this can bring, to solve difficult problems, etc, and therefore to perform actions such as writing novels (see further Ridley (2003) Chapter 8, Ridley (1993a) pp. 310 ff, Laland and Brown (2002) pp. 271 ff, and Dawkins (1982)). Indeed, culture is influenced by human genetic propensities, and it follows that human cognitive, affective, and moral capacities are the product of a unique dynamic known as *gene-culture coevolution* (Gintis 2007, Bowles and Gintis 2005, Gintis 2003, Boyd, Gintis, Bowles and Richerson 2003).

We may also note that the theory that genes set many goals for action does not mean that our behaviour is determined by genes. Modern evolutionary theory has led to the understanding that many traits, particularly behavioural ones, may have some genetic basis but that does not mean that they will inevitably appear, because much depends on the environment (Dawkins 1995, Ridley 2003). Further, part of the power of the theory of emotion described here is that in evolution genes specify rewards and punishers that are goals for action, but do not specify the actions themselves, which are flexible and can be learned.

Emotion Explained goes beyond the brain mechanisms of emotion with a treatment (in Chapter 4) of the many different learning processes that become engaged in relation to emotion. The book also includes a formal treatment (in Appendix 1) of reinforcement learning and temporal difference (TD) learning, which are increasingly being used to understand emotion-related learning, as well as its brain mechanisms.

Emotion Explained goes beyond the brain mechanisms of emotion with a treatment of the functions of affective states in motivated behaviour (including hunger, thirst, and sexual behaviour), and indeed proposes a fundamental and simple relation between emotion and motivation. The role of sexual selection in the evolution of affective behaviour is included in Chapter 9.

The book has an integrated section on decision-making (in Chapter 11), and includes links to the developing new field of neuroeconomics.

At the same time, *Emotion Explained* does consider research on how emotion is implemented in the brain, including much new research in the areas of neurophysiology, and functional neuroimaging and clinical neuropsychology in humans. This treatment of the brain mechanisms of emotion is important not only for providing a basis for understanding disorders of emotion, but also turns out to be important in unravelling the many different ways in which emotions can influence our behaviour, because the different brain mechanisms themselves are being unravelled. The book includes a new theory of how the orbitofrontal cortex supports rapid reversals of emotional behaviour, by using a short term memory network for the current rule which acts in a biased competition mode to influence neurons known to be present in the orbitofrontal cortex. This helps to provide a contrast between the functions of the orbitofrontal cortex and amygdala in emotion. A description of the theory is given in Chapter 4, and a formal treatment of how the system operates is given in Appendix 2.

Appendix 2 also shows how it is possible to model the processing involved in emotional learning from the synaptic and neuronal level up through the neuronal network level to predict fMRI neuroimaging signals and behaviour, and thus illustrates a foundation for linking the many different levels of investigation of the brain mechanisms of emotion into a consistent account of precisely how findings at these different levels of exploration are related to each other. This cross-disciplinary approach is a feature of this book. Appendix 1 includes a treat-

ment of autoassociation attractor networks that can maintain stable activity in a brain region, and shows how interacting attractor networks help to provide a foundation for understanding the interactions between mood, and cognition and memory.

The book links to research in psychiatry, with for example discussions of the impulsive behaviour that is a feature of borderline personality disorder, and to research in neurology, with for example assessment of the effects on emotion of damage produced by discrete lesions of the human brain.

Emotion Explained also goes beyond the brain mechanisms involved in emotion, by addressing (in Chapter 10) emotional feelings, part of the much larger problem of consciousness. One issue developed here is the concept that there is a credit assignment problem if a multiple step plan does not succeed, and that higher order thoughts provide a solution to this problem. The book also describes many recent functional neuroimaging investigations in which it has been possible to show that the activations of some brain regions are directly correlated with subjective feelings of affective state.

 Part of the material described in the book reflects work done over many years in collaboration with many colleagues, whose tremendous contributions are warmly appreciated. The contributions of many will be evident from the references cited in the text. In addition, I have benefited enormously from the discussions I have had with a large number of colleagues and friends, many of whom I hope will see areas of the text that they have been able to illuminate. Much of the work described would not have been possible without financial support from a number of sources, particularly the Medical Research Council of the UK, the Human Frontier Science Program, the Wellcome Trust, the McDonnell-Pew Foundation, and the Commission of the European Communities.

The book was typeset in Latex using the WinEdt editor by the author.

The cover shows part of the picture 'Psyche Opening the Door into Cupid's Garden' painted in 1904 by John William Waterhouse.

Updates to the publications cited in this book are available at http://www.cns.ox.ac.uk.

Edmund T. Rolls dedicates this work to the overlapping group: his family, friends, and colleagues: *in salutem praesentium, in memoriam absentium.*

Contents

6 Thirst

6.1 Introduction

In this Chapter, the systems that control thirst are described. These systems operate analogously to those involved in the control of feeding, although in the case of thirst the actual stimuli that initiate the thirst and drinking are relatively simple and prescribed, and so the way in which these signals control the motivated behaviour can be analysed quite precisely. For comparison, in Chapter 9 we consider the processing of rewards relevant to sexual behaviour, in which the conditions that initiate the drive are not simply homeostatic to maintain the internal milieu.

We focus on the rewards relevant to thirst and drinking. In the case of thirst there are internal signals that indicate that there is a need for water. The water is a reward, in that the organism will work to obtain the water. The signals that make the water rewarding originate internally. In the case of thirst, the internal signals reflect the volumes of the cellular and extracellular fluid. Thirst and drinking operate to maintain the constancy of the internal milieu. The internal signals operate to alter the reward value that water has for the thirsty organism. The reward signals are conveyed primarily by the taste and sight of water.

In this Chapter, we will consider where in information processing in these sensory systems the sensory stimulation produced by water is decoded not just as a physical stimulus, but is coded in terms of its reward value. An important aspect of brain organization is that these two aspects of information processing are kept separate, at least in primates including humans. Another important aspect of brain organization for this type of reward is that the learning of which visual stimuli are water, or are associated with water, takes place in specialized parts for the brain of this type of learning, and takes place after analysis of what the stimulus is.

Thirst is a sensation normally aroused by a lack of water and associated with a desire to drink water. The mechanisms involved in the control of drinking are useful to study, not only because of their medical relevance, but also because the stimuli that lead to drinking can be identified, measured and manipulated, so allowing the basis of a relatively complex, motivated behaviour to be analysed. The type of control of the reward value produced by the taste of water being modulated by internal thirst signals is analogous to the control of the reward value of the taste of food by internal hunger and satiety signals. However, thirst is a useful case to study because the internal signals that control thirst can be defined and precisely measured. A summary of the control signals for thirst is provided in Section 6.6 and Fig. 6.8 on page 286.

Body water is contained within two main compartments. The intracellular water accounts for approximately 40% of body weight, and the extracellular water is approximately 20% of body weight, divided between the blood plasma (the blood without the cells) (5% of body weight) and the interstitial fluid (the fluid between/outside the cells of the body and not in the blood vascular system) (15% of body weight) (see Fig. 6.1). After water deprivation, significant depletions of both the cellular and extracellular fluid compartments are found. To discover whether changes in either or both fluid compartments can act as stimuli for drinking,

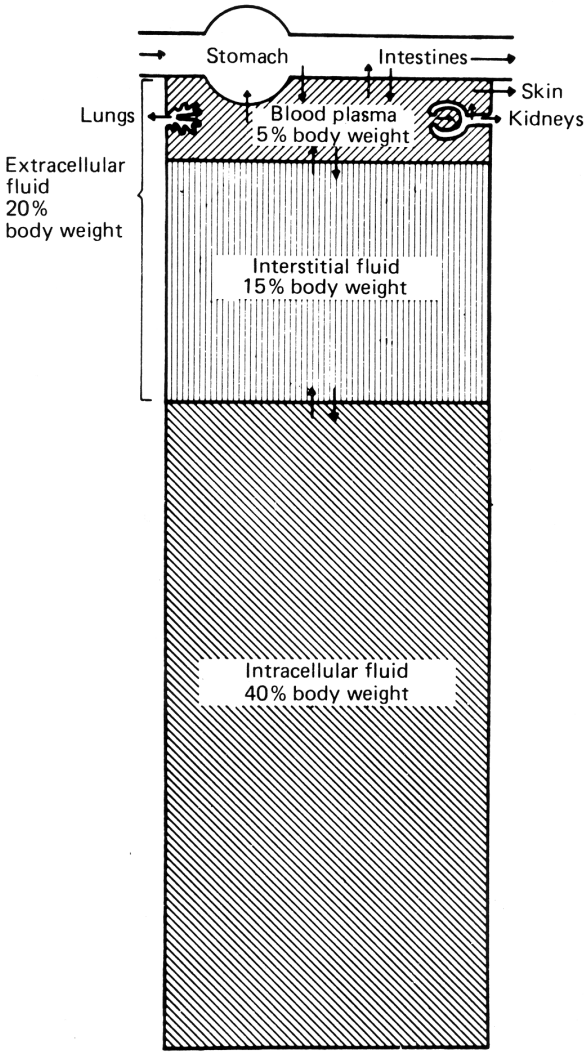

Fig. 6.1 Body water compartments. Arrows represent fluid movement. (After Rolls and Rolls 1982)

effects of selective depletion of one of the compartments on drinking, and the mechanisms activated, have been investigated as described below. References to original sources are contained in Rolls and Rolls (1982a), Rolls, Wood and Rolls (1980a), Grossman (1990), and Fitzsimons (1992).

6.2 Cellular stimuli for drinking

The drinking that occurs when the body fluids become concentrated due to net water loss or the ingestion of foods rich in salts such as meat appears to be initiated by cellular dehydration,

leading to cell shrinkage. Evidence for this is that the administration of concentrated sodium chloride solution leads to withdrawal of water from the cells by osmosis and produces drinking. (Osmosis is the process by which water may be withdrawn through the semipermeable membrane of cells if the concentration of salts and other osmotically active substances outside the cells is increased.) The effective change appears to be cellular dehydration and not an increase in absolute osmotic pressure (i.e. osmolality, as measured by freezing-point depression), in that administration of hypertonic substances such as sodium chloride and sucrose, which remain outside the cells and therefore cause cellular dehydration by osmosis, stimulates drinking. In contrast, similar concentrations of substances such as glucose, urea, and methylglucose, which cross the cell membrane and therefore do not lead to cellular dehydration, stimulate little or no drinking.

Increases in sodium concentration rather than cellular dehydration might be thought to be the thirst stimulus, but this seems unlikely since drinking is stimulated by the application of sucrose (which withdraws water from cells but does not raise sodium concentration) either directly to brain tissue (Blass and Epstein 1971, Peck and Novin 1971) or into the cerebral ventricles.

The degree of cellular dehydration must be monitored accurately, because sufficient water is consumed to dilute administered hypertonic sodium chloride solutions to the same concentration as the body fluids, that is to the same effective osmotic pressure (isotonicity).

Cellular dehydration as a stimulus for drinking is sensed centrally, in the brain, rather than peripherally, in the body, in that low doses of hypertonic sodium chloride (or sucrose) infused into the carotid arteries, which supply the brain, produced drinking in the dog. Peripheral infusions of the same magnitude had no effect on drinking (Wood, Rolls and Ramsay 1977).

The brain regions in which cellular dehydration is sensed and leads to drinking appear to be near or lie in a region extending from the preoptic area through the hypothalamus, and including tissue surrounding the anteroventral part of the third ventricle, to the zona incerta posteriorly (Fig. 6.2). In these regions (but not in other brain regions) injections of small volumes of mildly hypertonic sodium chloride or sucrose lead to drinking, which at least at some sites is motivationally specific, as drinking, but not eating, is elicited (Blass and Epstein 1971, Peck and Novin 1971). Consistent with the hypothesis that these brain regions are involved in drinking in response to cellular dehydration, small lesions here can specifically impair drinking in response to cellular thirst stimuli yet leave drinking in response to other thirst stimuli intact, although more non-specific effects of the lesions are common (Rolls and Rolls 1982a).

6.3 Extracellular thirst stimuli

6.3.1 Extracellular stimuli for thirst

Thus far we have considered only the effect of loss of fluid from inside cells on thirst. Although the amount of fluid in the extracellular fluid (ECF) compartment is less than that in the cells, it is vital for the organism that the ECF be conserved to avoid debilitating changes in vascular fluid volume and pressure. The effects of loss of extracellular fluid include fainting, caused by insufficient blood reaching the brain. In addition to the physiological and hormonal mechanisms that contribute to the maintenance of the ECF volume [e.g. baroreceptor reflexes stimulated by a fall in blood pressure, antidiuretic hormone (ADH) (which reduces

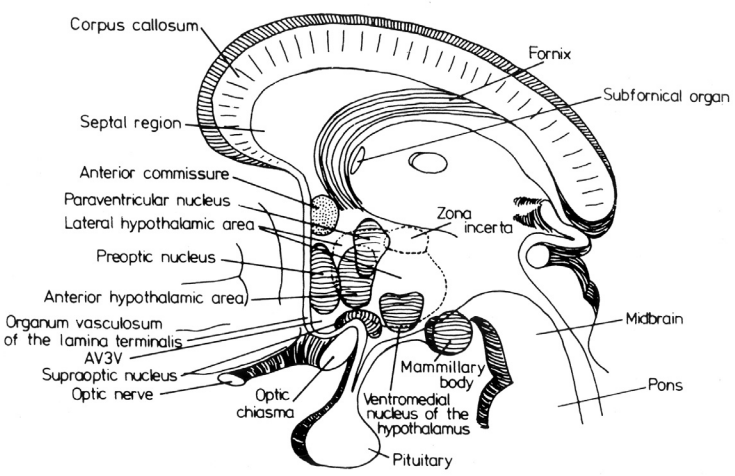

Fig. 6.2 Sagittal three-dimensional representation of the brain to illustrate some brain regions implicated in the control of drinking. AV3V: anteroventral region of the third ventricle. (After Rolls and Rolls 1982)

the excretion of water in the urine), and aldosterone (which reduces the excretion of sodium ion in the urine)], the behavioural response of drinking ensures that plasma volume does not fall to dangerously low levels.

The extracellular compartment has two components: the intravascular which contains the plasma, and the extravascular or interstitial fluid. These two components are in equilibrium and the receptors for controlling the ECF volume are located within the vasculature. ECF volume can become depleted in a variety of clinical conditions, which are accompanied by the loss of isotonic fluid as a result of vomiting, diarrhoea, or blood loss. (Isotonic fluid is fluid that is at the same 'strength' or effective osmotic pressure as the body fluids.) Significant ECF volume depletion will cause the release of antidiuretic hormone, which will reduce renal fluid loss. There might also be a need to replenish lost fluid, and it is advantageous that thirst often follows the ECF depletion in these clinical conditions.

There are several ways that ECF volume can be depleted experimentally in order to study the role of ECF volume in thirst. Obvious methods include haemorrhage, lowering the sodium content of the diet, and encouraging excessive sweating, urine production, or salivation, depending on the species being tested. However, ECF can be removed quickly and simply by injecting high concentrations of colloids (gum acacia or polyethylene glycol) either into the peritoneal cavity or subcutaneously. Isotonic fluid accumulates around the colloid, thereby depleting the ECF. Such depletion leads to a reduction in urine flow, and an increase in water intake that is related to the magnitude of the depletion. Some hours after the onset of thirst, a marked appetite for sodium develops and the ingestion of sodium restores the volume and composition of the ECF to normal.

The drinking that follows ECF depletion could be mediated by receptors in the vasculature. The role of such putative receptors in thirst can be studied by either constricting or expanding blood vessels in regions where such manipulations would be interpreted as under- or over-filling. Such studies have indicated that the receptors for extracellular thirst are located in two

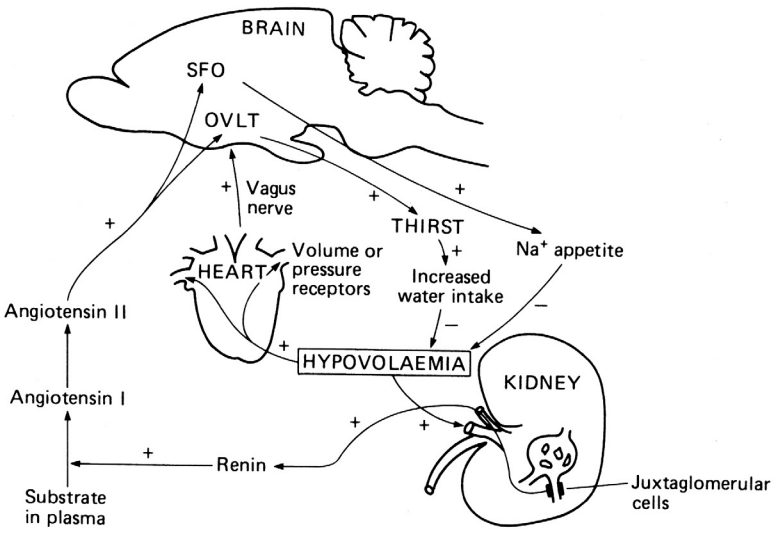

Fig. 6.3 A summary of the mechanisms involved in extracellular thirst. SFO, subfornical organ; OVLT, organum vasculosum of the lamina terminalis. (After Rolls and Rolls 1982)

main regions of the vasculature, in and around the kidneys and the heart (see Fig. 6.3), as shown by the following evidence.

6.3.2 Role of the kidney in extracellular thirst: the renin–angiotensin system

In the rat, ligation of the inferior vena cava, which reduces venous return to the heart and reduces arterial blood pressure, leads to a marked increase in water intake and a positive fluid balance due to decreased urine flow. If both kidneys are removed before ligation, water intake is significantly reduced, which suggests that an essential thirst stimulus following caval ligation could be a reduction in blood pressure to the kidneys. In order to test this hypothesis, Fitzsimons reduced the pressure to the kidneys by partially constricting the renal arteries, and found that water intake increased (see Fitzsimons (1992)).

When reductions in blood pressure or volume are sensed by the juxtaglomerular apparatus in the kidneys, the enzyme renin is released. Renin acts on substrate in the plasma to form angiotensin I, which is converted to angiotensin II, a vasoactive octapeptide (see Figs. 6.2 and 6.3). Angiotensin II is an active dipsogen in that intravenous infusions stimulate copious drinking (Fitzsimons and Simons 1969).

The receptors for angiotensin-induced drinking are located in the central nervous system, since injections into localized brain regions of doses of angiotensin at least 1000 times smaller than those required peripherally stimulate rats in fluid balance to drink large quantities of water (Epstein, Fitzsimons and Rolls 1970). Not only is angiotensin very potent, it is also very specific. Drinking is the only behavioural response that follows its administration and

this drinking is highly motivated. A wide variety of species (including mammals, birds, and reptiles) have been shown to drink after administration of angiotensin (see Rolls and Rolls (1982a)).

Since the initial discovery that intracranial angiotensin stimulates drinking, much work has been aimed at locating precisely the receptive site(s) in the brain. Angiotensin does not cross the blood–brain barrier, but the circumventricular organs, which are located on the surface of the cerebral ventricles, are outside the blood–brain barrier. Several circumventricular organs have now been suggested as receptive sites for angiotensin, and one of these is the subfornical organ (SFO) (see Fig. 6.4). Local application of angiotensin to the SFO in very low doses (1.0 pg) can stimulate drinking, and lesions of the SFO or application to it of a competitive angiotensin receptor-blocking agent, at least in the rat, can abolish drinking in response to intravenous angiotensin without affecting drinking in response to cellular thirst stimuli (Simpson, Epstein and Camardo 1977). The SFO has been shown electrophysiologically to contain angiotensin-sensitive neurons (Phillips and Felix 1976), and anatomically to send projections to the medial preoptic area, the supraoptic nucleus, and the brain close to the anteroventral part of the third ventricle (AV3V) (Miselis, Shapiro and Hand 1979). Injections of low doses of angiotensin in the region of another circumventricular organ, the organum vasculosum of the lamina terminalis (OVLT) in the anteroventral part of the third ventricle (see Fig. 6.3), also elicit drinking (Phillips 1978). Relatively large lesions in this region, which included damage to fibres from the SFO, reduced drinking in response to angiotensin (and to hypertonic sodium chloride) (Buggy and Johnson 1977a, Buggy and Johnson 1977b, Thrasher, Brown, Keil and Ramsay 1980a, Thrasher, Jones, Keil, Brown and Ramsay 1980b). Thus there is reasonable evidence that there are specialized and localized regions of neural tissue in or near the SFO and the OVLT involved in drinking produced by angiotensin (see Rolls and Rolls (1982a)).

6.3.3 Cardiac receptors for thirst

Local changes in volume and pressure in and around the heart are involved in extracellular thirst. Reducing the blood flow to the heart by partially constricting the thoracic inferior vena cava in the dog (a method used to produce low-output experimental cardiac failure) markedly increased water intake, which led to excessive oedema (Ramsay, Rolls and Wood 1975). Inflation of a balloon in the abdominal inferior vena cava also led to drinking which was correlated with the maximal fall in central venous pressure, but some drinking still occurred after administration of an angiotensin receptor-blocking agent and presumably was mediated by cardiac receptors (Fitzsimons and Moore-Gillon 1980). It is still not clear precisely where such cardiac receptors are located, but it seems most likely that they are in the low-pressure (venous) circulation around the heart (see Fig. 6.3), since the compliance of these vessels is high, making them responsive to changes in blood volume. It is thought that the information from these receptors is carried to the central nervous system via the vagosympathetic nerves, which normally exert an inhibitory effect on thirst.

6.4 Control of normal drinking

It has been shown above that there are mechanisms by which depletion of the cellular or the extracellular fluid compartments can stimulate drinking. An important question is to what

extent these mechanisms are normally activated during thirst and drinking, whether produced by water deprivation, or occurring when there is free access to water. Perhaps habit is one factor normally important in the initiation of drinking, but are deficits in the body fluid compartments normally involved in the initiation of drinking?

To gain evidence on this, it is first important to know whether deficits in the body fluid compartments are produced, for example, by water deprivation. There are deficits in both fluid compartments produced by water deprivation (Rolls, Wood and Rolls 1980a, Rolls and Rolls 1982a). This is the case not only in the rat, dog, and monkey, but also in humans (Rolls and Rolls 1982a, Rolls, Wood, Rolls, Lind, Lind and Ledingham 1980b). Next, it is found that the deficit in the cellular fluid compartment is large enough to lead to drinking, as shown by threshold measurements determined for the initiation of drinking in response to cellular dehydration. For example, following infusions of sodium chloride in the monkey, the threshold increase in plasma concentration necessary to evoke drinking was found to be 7 mOsmol kg^{-1} H_2O, which was less than the increase produced by water deprivation for 24 h (Wood, Maddison, Rolls, Rolls and Gibbs 1980). Other evidence comes from repletion experiments. When, after water deprivation, intravenous water preloads were given that effectively abolished the cellular fluid deficit, drinking was reduced by 65% in the rat and by 85% in the monkey (Wood, Maddison, Rolls, Rolls and Gibbs 1980, Wood, Rolls and Rolls 1982). If the ECF deficit is corrected by intravenous infusions of isotonic sodium chloride, then drinking is reduced by 20% and 5% in the rat and monkey, respectively (see Rolls, Wood and Rolls (1980a)). Thus depletion of the fluid compartments is an important determinant of drinking after water deprivation, with the depletion in the cellular compartment being more important, particularly in the primate (see further Rolls, Wood and Rolls (1980a) and Rolls and Rolls (1982a)).

In humans, it was found that with free access to water, the osmotic and extracellular thresholds for the elicitation of thirst were not normally reached before the humans had water to drink (Phillips, Rolls, Ledingham and Morton 1984). Thus in humans, at least when working in an air-conditioned temperature-controlled environment, drinking may anticipate needs. This anticipation is likely to be at least partly based on learning, so that after some time, actual body fluid deficits would be avoided. Humans would thus learn to initiate drinking based on any stimuli that are associated later with thirst signalled by cellular or extracellular body fluid deficits. In this way, drinking might become conditioned to stimuli such as large meals, salty food, or hot temperatures and dry conditions, or even to time of day. Of course, the primary thirst signals would be important for setting up this learning, but after the learning, the drinking would occur to the conditioned stimuli, and the primary thirst signals would not be activated. One would expect the primary thirst signals to become activated again if conditions changed, an example of which might be moving from sedentary work in an air-conditioned environment to physical work outdoors in a hot country. As a result of the activation of primary thirst signals, new learning would produce appropriate conditioned drinking for the new conditions.

Another factor in humans that may lead to primary body fluid deficit signals being unusual is that there is frequently available a large set of attractive drinks, including soft drinks, tea, and coffee.

Another interesting aspect of thirst is that in humans it was found that infusions of angiotensin did not always elicit drinking (Phillips, Rolls, Ledingham, Morton and Forsling 1985). Moreover, large variations of angiotensin concentrations are found when a human

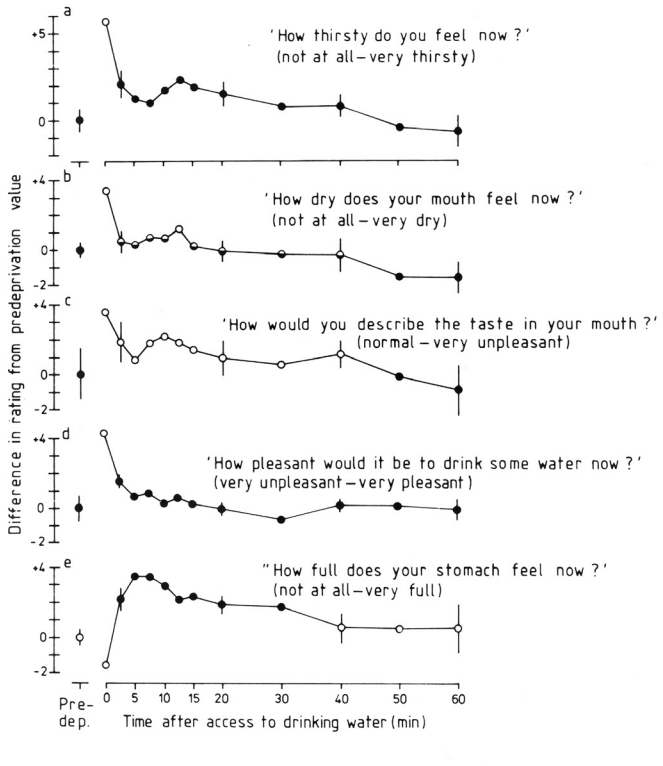

Fig. 6.4 The pleasantness of the taste of water is increased by water deprivation in humans, and decreases rapidly during drinking to satiety, before the water depletion of the body fluids has been completed. This is shown in the fourth graph from the top. In this diagram the effects of 24 h water deprivation on human subjective ratings of thirst and other sensations are shown by the difference between the predeprivation rating (pre-dep.) and the rating at time 0, taken 24 h later just before access to the water was given. The way in which the ratings changed after drinking started at time 0 is also shown. The significance of the changes relative to the value after 24 h water deprivation, at time 0, is indicated by closed circles ($P < 0.01$), half-filled circles ($P < 0.05$), or open circles (not significant). (After Rolls, Wood, Rolls, Lind, Lind and Ledingham, 1980; and Rolls and Rolls, 1982)

moves for example from lying down to standing up. The reason for this is that the change of posture in humans to standing upright on two legs produces a sudden drop in pressure in the renal arteries (as blood accumulates initially in the lower half of the standing body), and the release of angiotensin (stimulated by the reduced pressure in the renal arteries) produces vasoconstriction, which helps to compensate for the reduced blood pressure. Under these conditions (just standing up), thirst is not necessarily appropriate, and it may therefore be that the renin–angiotensin system is less important in humans than in other animals. It is nevertheless important to know about angiotensin in humans, for under some pathological conditions such as congestive heart failure, much angiotensin may be released as part of the body's attempt to compensate for some of the lack of fluid on the arterial side of the

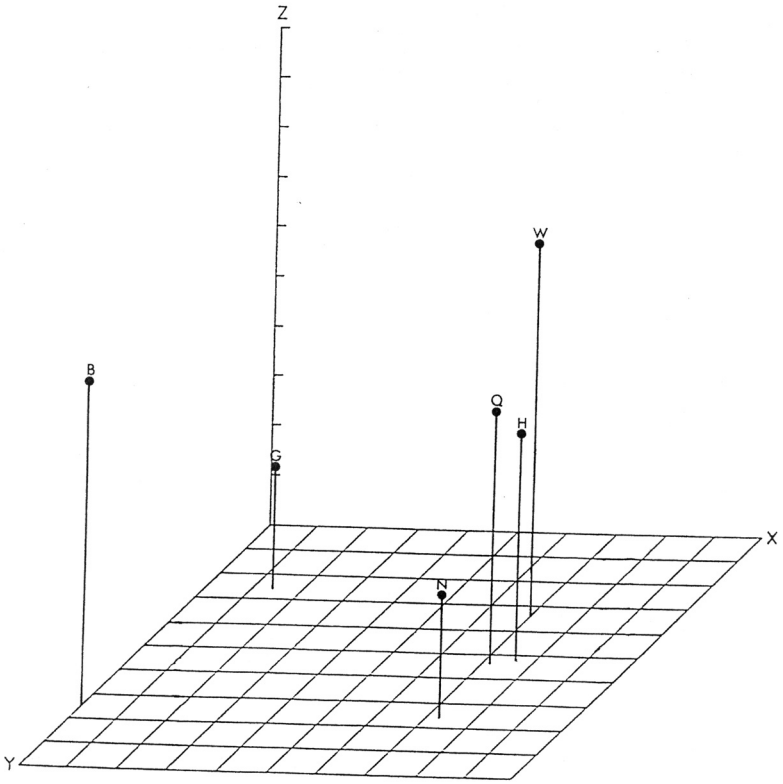

Fig. 6.5 The space produced by multidimensional scaling (MDS) of the responses of primate orbitofrontal cortex neurons to different tastes. The representation of water (W) is well separated from that of the prototypical tastes glucose (G), salt (N), bitter (Q, quinine) and sour (H, HCl). B, Blackcurrant juice. (After Rolls, Yaxley and Sienkiewicz 1990)

circulation (see Fitzsimons (1992)). However, to the extent that such pathologically high levels of angiotensin may produce thirst and lead to drinking, this drinking is inappropriate, for it may merely exacerbate the problem. Under these conditions, appropriate clinical care might include monitoring of water and fluid intake, to ensure that it is not excessive.

6.5 Reward and satiety signals for drinking

Drinking still occurs when ingested water is allowed to drain from a fistula in the oesophagus, stomach or duodenum. This is found in the rat, dog, and monkey (Rolls, Wood and Rolls 1980a, Rolls and Rolls 1982a, Gibbs, Rolls and Rolls 1986), and indicates that the reward for drinking is provided by oropharyngeal (and other pregastric) sensations such as the taste of water (at least in the first instance; compensatory learning may occur after prolonged experience). In fact, even a small quantity (e.g. 0.1 ml) of water delivered orally is sufficient to reinforce drinking, whereas much more water (e.g. 1–2 ml) must be delivered for the rat to learn a response in order to deliver water intragastrically (Epstein 1960) or intravenously

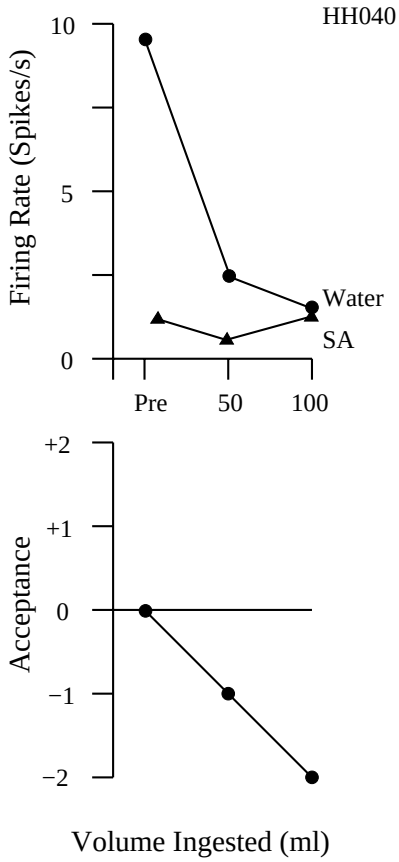

Fig. 6.6 An orbitofrontal cortex neuron in the monkey responding to the taste of water when thirsty, and gradually responding less to the taste of water during drinking to satiety. SA, spontaneous activity of the neuron; Pre, the firing rate before satiety was produced, by allowing the monkey to drink 100 ml water. The acceptability of the water is shown in the lower graph, on a scale from +2 indicating strong acceptance to –2 indicating strong rejection when satiety has been reached. (After Rolls, Sienkiewicz and Yaxley 1989.)

(Nicolaidis and Rowland 1974). This underlines the importance of exteroceptors in detecting and responding correctly to the presence of water, and shows that the presence of water in the gut or the dilution of plasma are not the primary rewards that normally control the animal's drinking.

A subjective analysis of the oropharyngeal control of drinking found that humans report (using a quantitative visual analogue rating scale) that the pleasantness of the taste of water is increased when they are thirsty as a result of water deprivation for 24 h, relative to the non-deprived condition (Rolls, Wood, Rolls, Lind, Lind and Ledingham 1980b) (see Fig. 6.4). It thus appears that oropharyngeal factors such as taste and swallowing maintain drinking and provide the incentive (or reward) for drinking.

There are neurons in the orbitofrontal cortex taste regions that respond to the 'taste' of water. Examples of this type of neuron are shown in Fig. 4.20 on page 98. The neuron responded much more to the taste of water than to other stimuli. There are many such neurons

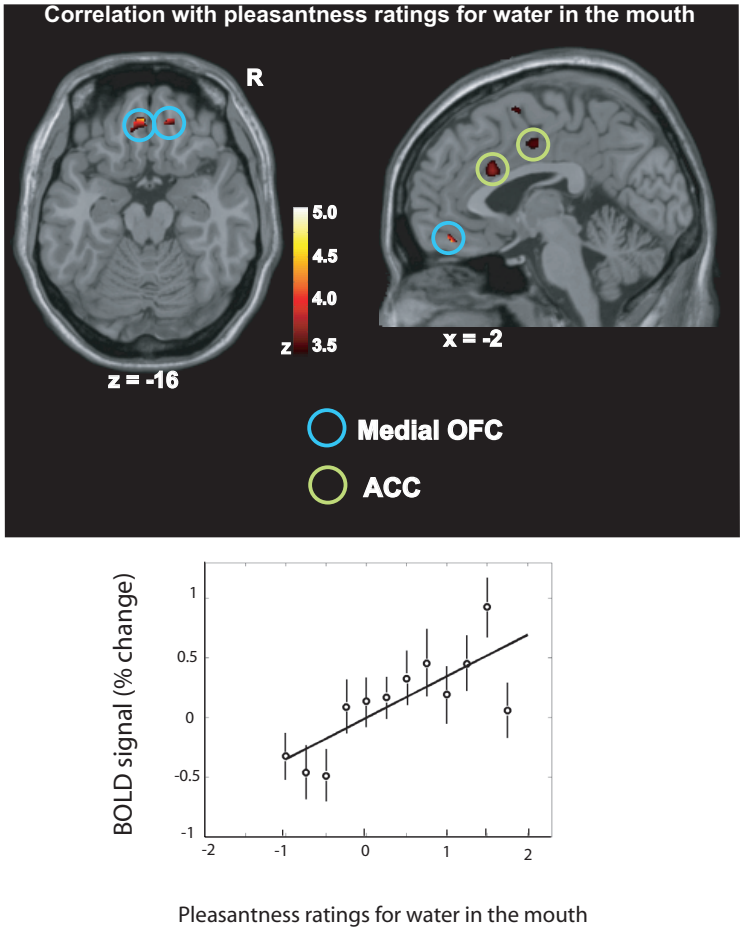

Fig. 6.7 Representation of the pleasantness of the taste of water in the human brain. Correlations with the pleasantness of the taste of water in a group random effects analysis. Top left: Regions of the medial caudal orbitofrontal where the activation was correlated with the subjective pleasantness ratings of water throughout the experiment. Bottom: A scatter plot showing the values of the BOLD signal in the medial orbitofrontal cortex (mean across subjects, ± s.e.m.), with the regression line shown. Top right: The regions of anterior cingulate cortex (ACC) where activation was correlated with the subjective pleasantness ratings of water given throughout the experiment. (After DeAraujo, Kringelbach, Rolls and McGlone, 2003.) (See colour plates section.)

in the orbitofrontal cortex (Rolls, Yaxley and Sienkiewicz 1990). Although there might not be water receptors per se on the tongue, the presence of water in the mouth may be signalled by the presence of non-viscous liquid in the mouth, and the absence of firing of sweet, salt, bitter, sour, and umami neurons. (The saliva in the mouth will be diluted when water is in the mouth.) In any case, the processing that has taken place by the time taste information reaches the orbitofrontal cortex results in a population of neurons that conveys information about the presence of water in the mouth, and that is approximately as large a population as that devoted to the other prototypical tastes sweet, salt, bitter, and sour (Rolls, Yaxley and

Sienkiewicz 1990).

The coding provided by these populations of taste-responsive neurons in the orbitofrontal cortex can be visualized using multidimensional scaling (MDS), as shown in Fig. 6.5. MDS is based on a distance measure of the representations provided by different neurons. It is based, for example, on the correlations between the response profiles of different neurons to a set of stimuli. If all the different neurons respond similarly to two stimuli, they will be close together in the MDS space. If the different neurons have differences in their responses to the two stimuli, the stimuli will be far apart in the space. The results of MDS on a population of taste neurons in the orbitofrontal cortex is shown in Fig. 6.5. It can be seen that the prototypical taste stimuli are well separated from each other, and that water is well separated from each of the other stimuli, in at least some dimensions of the space. Thus the 'taste' of water is clearly represented as being separate from that of other tastes in the primate orbitofrontal cortex.

The representation of taste in the primate orbitofrontal cortex is probably of the reward value of the taste of water, in that the responses of these neurons to the taste of water is reduced to zero by feeding the monkey to satiety (see Fig. 6.6; Rolls, Sienkiewicz and Yaxley (1989b)). After the reward value of the taste of water has been decoded in the orbitofrontal cortex, the output systems that link to action may be analogous to those described in Chapter 5 for hunger. For example, there are neurons in the lateral hypothalamus of the monkey that respond to the taste of water if the monkey is thirsty (Rolls, Burton and Mora 1976, Rolls and Rolls 1982a, Rolls, Murzi, Yaxley, Thorpe and Simpson 1986, Rolls, Rolls and Rowe 1983b). There are also neurons in the primate lateral hypothalamus that respond in a motivation-selective way to the sight of a visual stimulus associated with the sight of water but not of food when both thirst and hunger are present (see Fig. 5.12).

The human orbitofrontal cortex also has a corresponding representation of the pleasantness of the taste of water, in that as shown in Fig. 6.7, activations in the orbitofrontal cortex and parts of the anterior cingulate cortex were correlated with the subjective pleasantness (but not intensity) ratings for water in the mouth (De Araujo, Kringelbach, Rolls and McGlone 2003b). In this investigation, the brain activations were measured to the delivery of water in the mouth while the subjects were thirsty, and then again after the subjects had drunk water to satiety. The pleasantness of the taste of the water was decreased by drinking it to satiety, and the brain activations in the orbitofrontal cortex and cingulate cortex were correlated with the changes of the subjective pleasantness of water in the mouth. The control solution was a tasteless solution with the same ionic components as saliva.

In the termination of drinking, gastric and post-gastric factors such as gut stimulation by water, and the systemic effects of absorbed water are important, and oropharyngeal factors are of less importance. If, for example, drinking is measured with an oesophageal, gastric or duodenal fistula open, then much more water (e.g. 1.5–10 times) is consumed than normally or when the fistula is closed (Maddison, Wood, Rolls, Rolls and Gibbs 1980, Rolls, Wood and Rolls 1980a). Gastric distension appears to be one factor in satiety, for if drinking is allowed to terminate normally in the monkey, and then a gastric cannula is opened to allow water in the stomach to drain out, drinking starts again very promptly (Maddison, Wood, Rolls, Rolls and Gibbs 1980). Gastric distension can only operate normally if ingested water reaches the intestine to inhibit gastric emptying, because excessive drinking occurs with a duodenal fistula open (Maddison, Wood, Rolls, Rolls and Gibbs 1980). Gut stimulation by water, and possibly activation of immediately post-absorptive hepatic-portal mechanisms, may also contribute to satiety, because intraduodenal infusions of water are relatively more effective in terminating

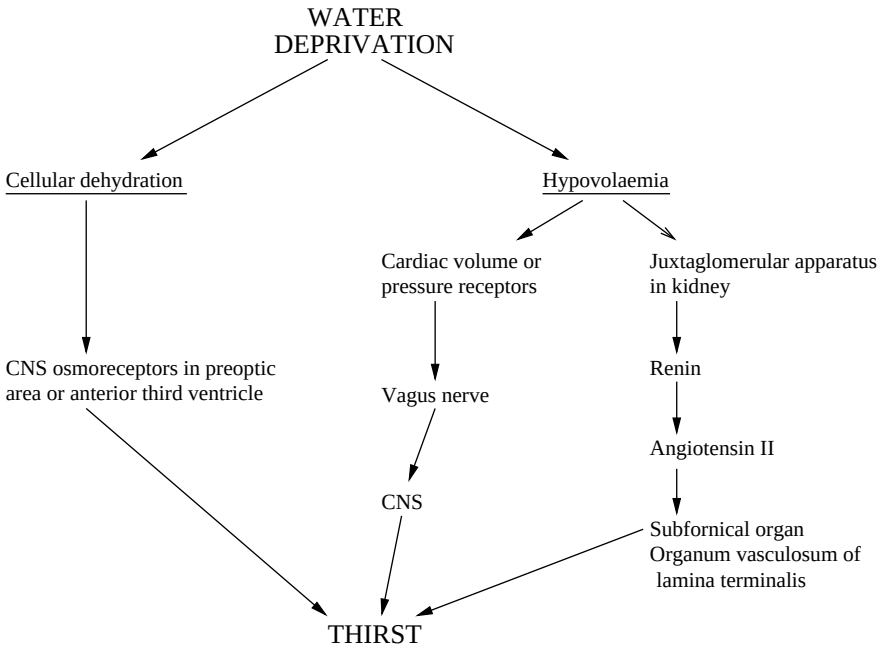

Fig. 6.8 A summary of the factors that can lead to drinking after water deprivation. (After Rolls and Rolls 1982)

drinking than intravenous infusions (Wood, Maddison, Rolls, Rolls and Gibbs 1980).

In the monkey and other relatively rapid drinkers such as the dog and human, systemic dilution produced by ingested water is not rapid enough to account for the termination of drinking, although, within 15–20 minutes after access to water, dilution of the body fluids is occurring (Rolls, Wood, Rolls, Lind, Lind and Ledingham 1980b, Rolls and Rolls 1982a). This dilution does at least contribute to satiety, since equivalent dilution produced by intravenous infusions of water reduces drinking (Wood, Maddison, Rolls, Rolls and Gibbs 1980).

The termination of drinking is best considered as the sequential activation of a number of contributing factors, starting with oropharyngeal stimulation by water (which appears to make a partial contribution to satiety as shown by observations that drinking with an oesophageal fistula open does usually stop in very rapid drinkers such as the dog (Towbin 1949); followed by gastric distension (which humans report subjectively to occur rapidly as satiety develops (Rolls, Wood, Rolls, Lind, Lind and Ledingham 1980b)); followed by gut and hepatic-portal stimulation by water; and finally systemic dilution and expansion (see Rolls, Wood, Rolls, Lind, Lind and Ledingham (1980b) and Rolls and Rolls (1982a)). Thus the reward value of the taste of water can be reduced by preabsorptive factors such as gastric distension, and later systemic dilution can contribute to satiety.

6.6 Summary

(see Fig. 6.8)

Drinking can be initiated by depletion of either the cellular or extracellular fluid compartments.

Both cellular and extracellular thirst stimuli (i.e. cellular dehydration and hypovolaemia) are produced by water deprivation in a variety of mammalian species, including man. Experiments in which the deficits in the fluid compartments are selectively repleted indicate that changes in both compartments contribute to drinking following water deprivation, but that changes in the cellular compartment are the more important.

Cellular dehydration as a thirst stimulus is indicated by the shrinkage of cells in or near the preoptic area of the brain.

Extracellular depletion as a thirst stimulus is indicated by activation of the renin–angiotensin system, and by signals from volume receptors in the low-pressure circulation on the venous side of the heart. Angiotensin is sensed by neurons in the subfornical organ, which have connections to a brain region close to the preoptic area.

Drinking is maintained or reinforced by oropharyngeal factors such as the taste of water, and it appears that the pleasantness of the taste of water in humans is influenced by the degree of thirst.

When water is consumed, the following changes occur in sequence and all contribute to the termination of drinking: oropharyngeal stimulation by water, gastric distension and gut stimulation by water, and finally systemic dilution.

7 Brain-stimulation reward

7.1 Introduction

Electrical stimulation at some sites in the brain is rewarding, in that animals including humans will work to obtain the stimulation. This phenomenon has been very useful in helping to understand the brain mechanisms that implement reward.

The discovery that rats would learn to stimulate electrically some regions of the brain was reported by Olds and Milner (1954). Olds noticed that rats would return to a corner of an open field apparatus where stimulation had just been given. He stimulated the rat whenever it went to the corner and found that the animals rapidly learned to go there to obtain the stimulation, by making delivery of it contingent on other types of behaviour, such as pressing a lever in a Skinner box or crossing a shock grid (Olds 1977) (see Fig. 7.1).

The electrical stimulation is usually delivered through electrodes insulated to within 0.1–0.5 mm of the tip and permanently implanted so that the tip is in a defined location in the brain. The stimulation usually consists of pulses at a frequency of 50–100 Hz delivered in a train 300–500 ms long. At self-stimulation sites the animal will repeatedly perform the operant response to obtain one train of stimulation for each press. The rate of lever pressing provides a measure of the self-stimulation behaviour. The phenomenon can be called brain-stimulation reward because the animal will work to obtain the stimulation of its brain. Brain-stimulation reward has been found in all vertebrates tested. For example, it occurs in the goldfish, pigeon, rat, cat, dog, monkey, and humans (Rolls 1975). Brain-stimulation reward can also refer to reward produced by injections of pharmacological agents into the brain. For example, animals will learn to inject small amounts of amphetamine to certain parts of the brain. Pharmacological aspects of reward are described in Chapter 8.

7.2 The nature of the reward produced

One way in which the nature of the reward produced by brain stimulation can be tested in animals is by altering the drive (e.g. the hunger) of the animal to determine how this influences the reward produced by the stimulation. At some brain sites, for example in the lateral hypothalamus, a reduction of hunger can reduce the self-stimulation rate (Hoebel 1969, Hoebel 1976). As a reduction of hunger reduces both food reward (in that the animal will no longer work for food), and brain-stimulation reward at some brain sites, it is suggested that the stimulation at these brain sites is rewarding because it mimics the effect of food reward for a hungry animal (Hoebel 1969, Rolls 1975). This modulation of brain-stimulation reward by hunger is found at lateral hypothalamic sites (Rolls, Burton and Mora 1980c) and of all sites I have tested, most profoundly in the orbitofrontal cortex (Mora, Avrith, Phillips and Rolls 1979).

It is important to note that this modulation by satiety is not just a general effect on performance of, for instance, drowsiness, because a reduction of hunger may reduce self-stimulation

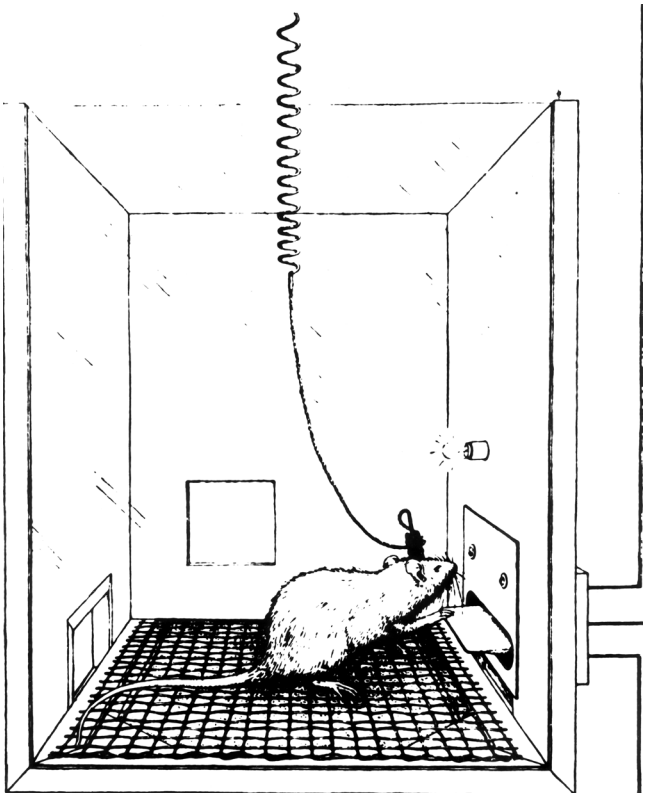

Fig. 7.1 A rat pressing a lever in order to obtain brain-stimulation reward. The reward is provided by a 0.5 s train of pulses of stimulation at typically 50–100 Hz delivered each time the rat presses the bar. (After Olds 1956.)

at some sites but not at others (Rolls 1975). Further, at some sites hunger may facilitate self-stimulation, while at other sites thirst may facilitate self-stimulation. For example, in an experiment by Gallistel and Beagley (1971) rats chose stimulation on one electrode if they were hungry and on a different electrode if they were thirsty (see Fig. 7.2). One interesting and useful feature of this experiment is that a choice rather than a rate measure of the reward value of the brain stimulation was used. The advantage of the choice measure is that any general effect such as arousal or drowsiness produced by the treatment which could affect response rate has a minimal effect on the outcome of the experiment. The experiment shows that at some sites brain-stimulation reward can be equivalent to a specific natural reward, such as food for a hungry animal or water for a thirsty animal.

Support for this view that brain-stimulation reward can mimic the effects of a natural reward such as food comes from neurophysiological experiments described below in which brain-stimulation reward and food reward have been shown to activate the same neurons in the hypothalamus.

At some other sites, the brain-stimulation reward produces effects that mimic those of sexual rewards. For example, at sites in the posterior hypothalamus but not in the lateral hypothalamus in male rats, castration decreases the self-stimulation, and subsequent androgen

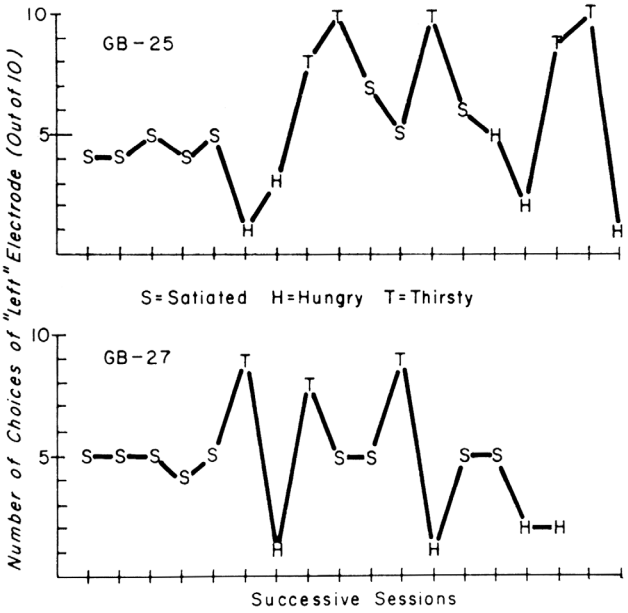

Fig. 7.2 Water and food reward effects produced by electrical stimulation of the brain in two rats. If the rats were thirsty (T) they chose to press a lever that delivered electrical stimulation to one brain site, and if they were hungry (H) they chose to press the other lever that delivered stimulation to another brain site. If the rats were satiated (S) for both food and water, then the preference for the two sites was approximately equal. (Reprinted with permission from Gallistel and Beagley 1971.)

replacement injections produced a differential facilitation of the posterior hypothalamic self-stimulation (Caggiula 1970, Olds 1958, Olds 1961).

At other sites natural drives such as hunger and thirst do not modulate self-stimulation, so that some other reward process, perhaps more related to emotion as described next, must underlie the reward produced (Rolls 1975).

A different type of evidence on the nature of the reward produced by electrical stimulation of the brain comes from direct reports of the sensations elicited by the stimulation in humans. During the investigation of, or treatment of, epilepsy, tumours or Parkinson's disease, electrical stimulation has been given to localized brain regions to evaluate the functioning of particular regions. Sem-Jacobsen (1968) and Sem-Jacobsen (1976) reported on the effects of stimulation at 2639 sites in 82 patients. Pleasant smells were evoked by the stimulation at nine sites, and unpleasant at six. Pleasant tastes were evoked at three sites, and unpleasant at one. Sexual responses were elicited at two sites. These types of finding are consistent with the food-related and other effects of the stimulation at some sites inferred from experiments with animals.

The relative paucity of reports of this type in humans may be because brain sites in the temporal and frontal lobes are usually investigated and the electrodes do not normally reach the basal regions such as the hypothalamus that are often investigated in animals.

More common in humans are reports that mood changes are elicited by stimulation at some sites. In Sem-Jacobsen's series, at 360 points the patients became relaxed, at ease, had a feeling of well-being and/or were a little sleepy (classed as Positive I). At 31 sites the patients in addition showed enjoyment, frequently smiled and might want more stimulation (Positive

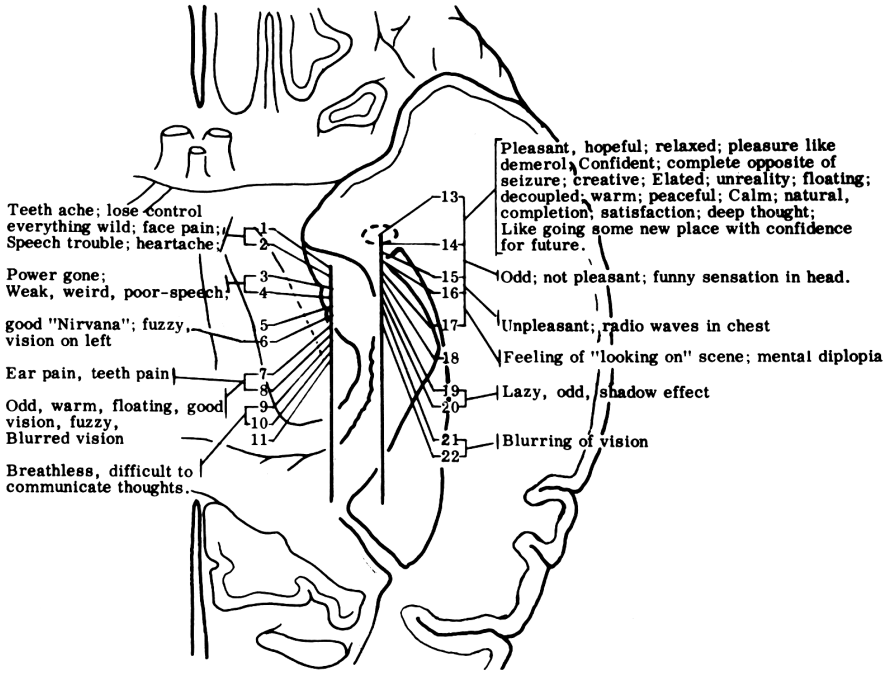

Fig. 7.3 Summary of subjective states evoked by electrical stimulation at different sites along two tracks in the human temporal lobe on a diagrammatic representation of the stimulating points. (Reprinted from Stevens, Mark, Ervin, Pacheco and Suematsu 1969)

II). At eight sites (in seven patients) the patients laughed out loud, enjoyed themselves, positively liked the stimulation and wanted more (Positive III). These and other reports of mood changes were produced by the stimulation. Thus at some brain sites in humans electrical stimulation can produce mood changes, stimulation may be desired, and this may be associated with self-stimulation (Heath 1954, Heath 1963, Heath 1972, Bishop, Elder and Heath 1963, Stevens, Mark, Ervin, Pacheco and Suematsu 1969, Delgado 1976, Sem-Jacobsen 1976, Valenstein 1974, Halgren 1992). Examples of some of the effects produced by electrical stimulation in tracks made into the temporal lobe during neurosurgery are illustrated in Fig. 7.3.

The evidence available from animals and humans thus suggests that the nature of the reward produced at different self-stimulation sites depends on the site: at some sites (e.g. the lateral hypothalamus and the secondary taste cortex in the orbitofrontal region) the stimulation may be equivalent to a specific natural reward such as food for a hungry animal. At other sites the stimulation may produce more general changes in mood and may thus be desired. At other sites (e.g. some parts of the orbitofrontal cortex and amygdala) it is possible that the stimulation taps into brain systems concerned with learning about stimulus–reinforcer associations, where of course primary reinforcers must be represented, and where the output pathways must be capable of signalling (secondary) reinforcement if they are to implement the effects that secondary reinforcers have. This analysis makes it clear that brain self-stimulation may occur for any one of a number of reasons and that a single basis for brain-stimulation reward should not be expected.

It is now to the neural bases of brain-stimulation reward that we turn. We will be concerned not only with the neural mechanisms of brain-stimulation reward at different sites, but also with what can be learned about reward processes in the brain from studies of brain-stimulation reward.

For example, one question before us will be how it happens that animals will only work for food (i.e. find it rewarding) when they are hungry. Another question is why brain-stimulation reward continues for hours on end with no appearance of satiety. Is the elicitation of a reward by a sensory stimulus something that normally can continue indefinitely, and if so, how does the system normally arrange for any one reward not to dominate behavioural choice for long periods? Another question, examined in Chapter 8, will be how studies of the pharmacology of brain-stimulation reward relate to our understanding of the control of mood, and what they tell us about the neural basis of addiction.

7.3 The location of brain-stimulation reward sites in the brain

To understand the neural mechanisms of brain-stimulation reward it is first necessary to know where brain self-stimulation sites are located. One group is located along the general course of the medial forebrain bundle, passing lateral to the midline from the ventral tegmental area of the midbrain posteriorly, through the lateral hypothalamus, preoptic area and nucleus accumbens, toward the prefrontal cortex (orbitofrontal cortex in the monkey) anteriorly (Fig. 7.4) (Olds and Olds 1965, Rolls 1971c, Rolls 1974, Rolls 1975, Rolls 1976a, Rolls and Cooper 1974, Mora, Avrith and Rolls 1980, Rolls, Burton and Mora 1980c). Many cell groups and neural pathways follow this path or much of this general course. For example, there is the medial forebrain bundle itself, interconnecting forebrain and brainstem regions with hypothalamic and other diencephalic systems. There are fibres connected to neurons in prefrontal self-stimulation sites, which pass many self-stimulation sites in their course through the brain (Routtenberg, Gardner and Huang 1971, Rolls and Cooper 1973, Rolls and Cooper 1974). In addition there are dopamine-containing fibres in the mesolimbic and mesocortical systems ascending from cell group A10 in the ventral tegmental region to the ventral striatum and orbitofrontal cortex, as well as in the substantia nigra (cell group A9) coursing to the striatum (see Sections 8.3 and 8.4). It is likely that many neural systems are activated by electrodes in this group of sites and it is possible that stimulation of any one of a number of systems in this region may support self-stimulation.

A second group of self-stimulation sites is in limbic and related areas such as the amygdala, nucleus accumbens, and prefrontal cortex (orbitofrontal cortex in the monkey) (Rolls 1974, Rolls 1975, Rolls 1976a, Rolls, Burton and Mora 1980c, Mora, Avrith and Rolls 1980). This group of sites is highly interconnected neurophysiologically with the first group lying along the general course of the medial forebrain bundle, in that stimulation in any one of these reward sites activates neurons in the others in primates (Rolls, Burton and Mora 1980c) (see below).

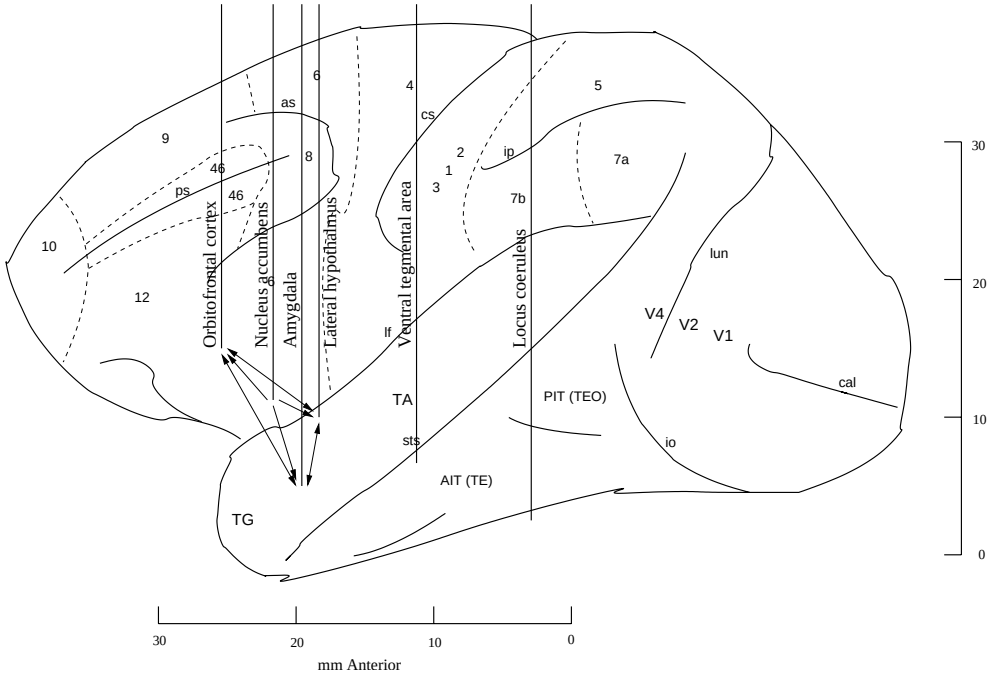

Fig. 7.4 Some brain sites in primates at which electrical stimulation of the brain can produce reward. The arrows indicate that stimulation at any one of these sites activates neurons in all of the other sites connected by arrows, as shown by Rolls, Burton and Mora (1980). The scales show the stereotaxic base planes. Abbreviations as in Fig. 4.1.

7.4 The effects of brain lesions on intracranial self-stimulation

Lateral or posterior hypothalamic self-stimulation rate is decreased (but not abolished) by small lesions in or near the medial forebrain bundle, particularly if the lesions are caudal to (i.e. behind) the self-stimulation electrode (Boyd and Gardner 1967, Olds and Olds 1969, Stellar and Stellar 1985). Ipsilateral, but not contralateral, lesions are effective. Thus a unilaterally organized system that can be disrupted particularly by posterior lesions at least modulates hypothalamic self-stimulation. Lesions that destroy most of the locus coeruleus do not abolish self-stimulation from regions anterior to it through which its fibres pass, so that it is unlikely that the cells of the locus coeruleus support self-stimulation even from these sites (Clavier 1976, Clavier and Routtenberg 1976). Cells in the dopamine A10 pathway are important for self-stimulation of some sites such as the ventral tegmentum, but not for self-stimulation of all sites, in that neurotoxic lesions of the dopamine inputs to the nucleus accumbens abolish self-stimulation of only some sites (Phillips and Fibiger 1989).

It is interesting to note that self-stimulation can occur after ablation of most of the forebrain in rats. Huston and Borbely (1973) were able to show this by requiring only a simple response of tail-raising (or lowering) which their forebrain-ablated rats were able to learn in order to obtain posterior hypothalamic stimulation (although extinction was impaired). This finding underlines the view that self-stimulation can occur because of the activation of one of a

number of systems, and suggests that the basic mechanisms for rewarded behaviour must be represented at a low level in the brain. Forebrain areas may be related to reward, not because they are essential for all rewarded behaviour, but because they are concerned with decoding complex sensory inputs and determining whether these inputs are associated as a result of previous learning with reward; and with executing complex, instrumental, motor responses to obtain reward (see below).

Evidence that neurons with cell bodies in the lateral hypothalamus are involved in the reward effects produced by stimulation there comes from studies in which neurotoxic lesions of the lateral hypothalamus (which damage cell bodies there but not fibres of passage such as the dopaminergic fibres) attenuate self-stimulation of the lateral hypothalamus (and of sites anterior to it) (Lestang, Cardo, Roy and Velley 1985). It is possible that descending lateral hypothalamic neurons that mediate reward synapse on to dopamine neurons in the ventral tegmental area, and that the dopamine connection is important in the reward produced (Wise 1989, Shizgal and Murray 1989). However, the dopamine connection does not appear to be an essential part of the substrate of lateral hypothalamic brain-stimulation reward, for unilateral 6-OHDA lesions of the dopamine cell bodies in the ventral tegmentum did not attenuate lateral hypothalamic self-stimulation (Phillips and Fibiger 1976, Fibiger, LePiane, Jakubovic and Phillips 1987).

7.5 The neurophysiology of reward

By recording from single neurons while stimulation is delivered at the threshold current to self-stimulation electrodes[16], it is possible to determine which neural systems are actually activated by brain-stimulation reward. In the rat it is clear that during hypothalamic self-stimulation, neurons in the prefrontal cortex, amygdala and some areas of the brainstem, as well as in the hypothalamus itself, are activated (Rolls 1974, Rolls 1975, Rolls 1976a, Ito 1976). In the monkey it has been found that neurons in the lateral hypothalamus, orbitofrontal cortex, amygdala, nucleus accumbens, and ventral tegmental area are activated during self-stimulation of any one of these sites or of the nucleus accumbens (see Fig. 7.4) (Rolls 1974, Rolls 1975, Rolls 1976a, Rolls, Burton and Mora 1980c). Thus in the monkey, there is a highly interconnected set of structures, stimulation in any one of which will support self-stimulation and will activate neurons in the other structures.

7.5.1 Lateral hypothalamus and substantia innominata

Mainly in the monkey, it has been possible to record in the alert, behaving animal from neurons activated by brain-stimulation reward, and to determine whether these neurons are also activated by natural rewards such as food given to the hungry animal or during learning. When recording in the lateral hypothalamus and substantia innominata (which is lateral and rostral to the lateral hypothalamus) from neurons activated by brain-stimulation reward, it was found that some neurons (approximately 13% in one sample of 764 neurons) altered their activity in relation to feeding (Rolls 1974, Rolls 1975, Rolls 1976a, Rolls 1979, Rolls, Burton and Mora 1980c). This is the same population of hypothalamic neurons with feeding-related

[16] The threshold current for self-stimulation is the minimum amount of current for a given stimulation pulse-width required to produce self-stimulation at a given self-stimulation site.

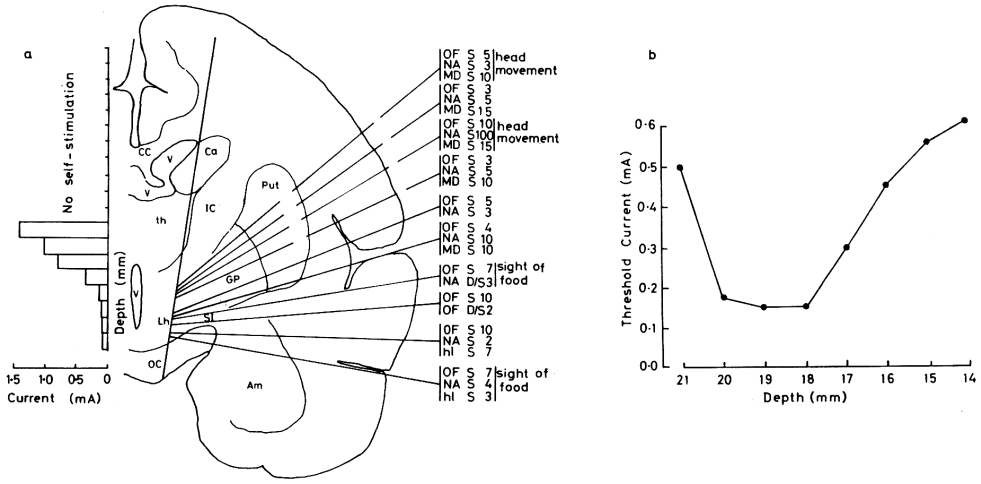

Fig. 7.5 a. Neurons activated by both brain-stimulation reward and the sight of food were found at the lower end of this microelectrode track in the macaque lateral hypothalamus. Neurons higher up the track in the globus pallidus were activated by brain-stimulation reward and also by head movements. The neurons were trans-synaptically (S) or possibly in some cases directly (D/S) activated with the latencies shown in ms from self-stimulation sites in the orbitofrontal cortex (OF), nucleus accumbens (NA), mediodorsal nucleus of the thalamus (MD), or lateral hypothalamus (hl). b. Self-stimulation through the recording microelectrode occurred with low currents if the microelectrode was in the hypothalamus close to the neurons activated by the sight of food. (From Rolls 1975; Rolls, Burton and Mora 1980.)

responses described in Chapter 5. Indeed, the neurons with feeding-related responses were discovered originally when we sought to determine what functions the hypothalamic neurons activated by brain-stimulation reward perform.

In the original sample of 764 neurons, some altered their activity only during the ingestion of some substances, so that their activity appeared to be associated with the taste of food. Many more of these neurons (approximately 11% of the total sample) altered their activity before ingestion started, while the animal was looking at the food (Rolls, Burton and Mora 1976, Rolls, Sanghera and Roper-Hall 1979a). The activity of this second set of neurons only occurred to the sight of food if the monkey was hungry (Burton, Rolls and Mora 1976), and becomes associated with the sight of food during learning (Mora, Rolls and Burton 1976b). Thus the activity of these neurons is associated with the sight and/or taste of food in the hungry animal, that is with the presentation of food reward.

To determine whether the activity of these neurons precedes, and could thus mediate, the responses of the hungry animal to food reward, their latency of activation was measured using a shutter that opened to reveal a food or a non-food-related visual stimulus (Rolls, Sanghera and Roper-Hall 1979a). The latency for different neurons was 150–200 ms, and compared with a latency of 250–300 ms for the earliest electrical activity recorded from the genioglossus muscle associated with the motor responses of a lick made to obtain food when the food-related visual stimulus was shown (see Fig. 5.10). (Upper motor neuron firing would occur in close temporal relation to the electromyogram recorded from this muscle.) Thus the motor response to the food could not result in the food-related activity of the hypothalamic neurons. This is consistent with the view that these neurons activated both by food reward and

brain-stimulation reward are involved in mediating the reactions of the animal to food. These reactions to the food reward include the initiation of feeding behaviour, as well as endocrine and autonomic responses to the food (Fig. 4.2).

These hypothalamic neurons only respond to the sight or taste of food when the monkey is hungry (Burton, Rolls and Mora 1976, Rolls, Murzi, Yaxley, Thorpe and Simpson 1986). This is part of the evidence that implicates these neurons in the reward produced by the sight or taste of food if hunger is present. It is also thus very interesting that self-stimulation in the lateral hypothalamus is reduced by feeding the monkey to satiety (Rolls, Burton and Mora 1980c). As noted earlier, this indicates that the reward produced by the electrical stimulation of the lateral hypothalamus is like food for a hungry monkey, in that the reward value of each is reduced by feeding the monkey to satiety. In an additional experiment, it was shown that the current passed through the microelectrode that had recorded from food-related neurons in the lateral hypothalamus was lowest when the electrode was at the depth of the feeding-related neurons (see Fig. 7.5) (Rolls 1975, Rolls, Burton and Mora 1980c).

Taken together, these results show that brain-stimulation reward of the lateral hypothalamus occurs because it activates and thus mimics the effects that food reward has on these neurons. In a reciprocal way, the fact that self-stimulation of a number of brain sites, including the lateral hypothalamus, activates these neurons also activated by food when the food is rewarding provides useful evidence that the firing of these neurons actually produced reward. This is one of the valuable outcomes of research on brain-stimulation reward – it helps to show whether the firing of neurons activated by natural rewards is causally related to producing reward, and does not reflect some other process produced by food, such as salivation to food.

It is also worth noting that hypothalamic self-stimulation does not depend on direct activation of dopamine neurons, in that the refractory periods of directly activated neurons that mediate lateral hypothalamic reward are in the region of 0.6–1.2 ms, whereas the refractory periods of the dopamine neurons, which are small and unmyelinated, are in the range 1.2–2.5 ms (Rolls 1971c, Rolls 1971a, Yeomans 1990). Further, dopamine does not appear to be an essential part of the substrate of lateral hypothalamic brain-stimulation reward, for unilateral 6-OHDA lesions of the dopamine cell bodies in the ventral tegmentum did not attenuate lateral hypothalamic self-stimulation (Phillips and Fibiger 1976, Fibiger et al. 1987).

7.5.2 Orbitofrontal cortex

The orbitofrontal cortex is one of the brain regions in which excellent self-stimulation is produced in primates (Mora, Avrith, Phillips and Rolls 1979, Phillips, Mora and Rolls 1979, Phillips, Mora and Rolls 1981, Rolls, Burton and Mora 1980c, Mora, Avrith and Rolls 1980). The self-stimulation is like lateral hypothalamic self-stimulation in that it is learned rapidly, and occurs at a high rate. It has been shown that the self-stimulation of the orbitofrontal cortex is hunger-dependent, in that feeding a monkey to satiety produces great attenuation of orbitofrontal cortex self-stimulation (Mora, Avrith, Phillips and Rolls 1979). Of all the brain-stimulation reward sites studied in the monkey, it is the one at which feeding to satiety has the most profound effect in reducing self-stimulation (Rolls, Burton and Mora 1980). The orbitofrontal self-stimulation pulses have also been shown to drive neurons strongly in the lateral hypothalamus with latencies of only a few ms (Rolls 1975, Rolls 1976a, Rolls, Burton and Mora 1980c). On the basis of these findings, it was suggested that orbitofrontal cortex stimulation in primates is rewarding because it taps into food-reward mechanisms.

This proposal has been greatly elaborated by the discovery of the way in which the primate orbitofrontal cortex analyses the stimuli that implement food reward (and other types of reward too). The investigations of the neurophysiology of the orbitofrontal cortex that led to these discoveries were prompted by the fact that the orbitofrontal cortex is a good site for brain-stimulation reward, and that lateral hypothalamic food-related neurons are activated by rewarding stimulation of the lateral hypothalamus (Rolls 1974, Rolls 1975, Rolls 1976a, Rolls 1976b, Rolls, Burton and Mora 1980c). The discoveries included the following, considered in more detail in Chapters 4 and 5:

1. The secondary taste cortex is in the orbitofrontal cortex (Rolls, Yaxley and Sienkiewicz 1990, Baylis, Rolls and Baylis 1994).

2. The representation in the secondary taste cortex is of the reward value of taste, in that the responses of taste neurons here (but not in the primary taste cortex) are reduced to zero when the monkey feeds himself or herself to normal, physiological satiety (Rolls, Sienkiewicz and Yaxley 1989b, Rolls, Scott, Sienkiewicz and Yaxley 1988, Yaxley, Rolls and Sienkiewicz 1988). There is also a representation of the reward value of the 'taste' of water in the primate orbitofrontal cortex (Rolls, Sienkiewicz and Yaxley 1989b), and activations in the human orbitofrontal cortex are correlated with the pleasantness of the water in the mouth (De Araujo, Kringelbach, Rolls and McGlone 2003b).

3. The reward value of olfactory stimuli is represented in the secondary and tertiary cortical olfactory areas in the primate orbitofrontal cortex (Critchley and Rolls 1996b), representations which are themselves built for some orbitofrontal olfactory neurons by association with the primary reinforcer of taste (Rolls, Critchley, Mason and Wakeman 1996b, Critchley and Rolls 1996b). The subjective pleasantness of odour is correlated with activations in the human orbitofrontal cortex (Rolls, Kringelbach and De Araujo 2003c, O'Doherty, Rolls, Francis, Bowtell, McGlone, Kobal, Renner and Ahne 2000).

4. The reward value of visual stimuli such as the sight of food is represented in the primate orbitofrontal cortex (Critchley and Rolls 1996b), and the learning of the representation of which visual stimuli are rewarding is built in the orbitofrontal cortex by visual-to-taste reward learning (Rolls, Critchley, Mason and Wakeman 1996b), which can occur in one trial, and be reversed in one trial, by neurons in the orbitofrontal cortex (Thorpe, Rolls and Maddison 1983, Rolls, Critchley, Mason and Wakeman 1996b).

5. There is a representation of the mouth feel of food, including information about the presence of fat, in the orbitofrontal cortex, mediated through the somatosensory system (Rolls, Critchley, Browning, Hernadi and Lenard 1999a, Verhagen, Rolls and Kadohisa 2003, De Araujo and Rolls 2004) (see Chapter 5). These sensory inputs converge on to some orbitofrontal neurons that represent the pleasantness or reward value of taste, and are themselves likely to make a major contribution to the evaluation of the palatability (reward value) of food in the mouth (Rolls, Critchley, Browning, Hernadi and Lenard 1999a, Rolls, Verhagen and Kadohisa 2003e). Activations in the human orbitofrontal cortex are correlated with the subjective pleasantness of food during investigations with a whole food of sensory-specific satiety (Kringelbach, O'Doherty, Rolls and Andrews 2003).

6. The pleasantness of touch is represented in the human orbitofrontal cortex (Rolls, O'Doherty, Kringelbach, Francis, Bowtell and McGlone 2003d).

7. Activations in the human medial orbitofrontal cortex correlate with abstract rewards such as monetary gain in a probabilistic monetary reward task (O'Doherty, Kringelbach, Rolls, Hornak and Andrews 2001a).

These discoveries thus extend the explanation of why orbitofrontal cortex electrical stimulation can produce reward. It does so by activating representations concerned with the reward value of a whole spectrum of rewarding sensory stimuli, including the taste, smell, and texture of food, the reward value of water, the reward value of touch, and also abstract rewards such as monetary gain.

The fact that brain-stimulation reward of the orbitofrontal cortex occurs supports the evidence that this region implements the reward value of sensory stimuli related to food, as well as to other stimuli. The orbitofrontal cortex may be related to reward not only because it represents the reward value of a number of primary reinforcers (e.g. taste and touch), but also because it is involved in learning associations between primary reinforcers and the stimuli (such as the sight of food) with which they are associated. For this pattern-association learning (and reversal) process, the orbitofrontal cortex must contain a representation of both the primary reinforcer and the to-be-associated (e.g. visual) stimulus (see Appendix 1). Moreover, the firing of neurons that convey the fact that a secondary reinforcer is reinforcing must themselves if activated produce reward, and this, as well as the activation of representations of primary reinforcers such as taste and touch, implements the reward value of electrical stimulation of the orbitofrontal cortex.

It is noted that in rats the reward value of what may be a corresponding though less developed region, the sulcal prefrontal cortex, does not depend on the integrity of the dopamine inputs to this region (Phillips and Fibiger 1989). This suggests that activation of neurons in the orbitofrontal cortex is the fundamental component of reward produced by activation of this region, and not any possible activation of dopamine neurons or dopamine inputs to the prefrontal cortex.

Moreover, the findings considered above are consistent with the possibility that one way in which dopaminergic activation produced by the psychomotor stimulants such as amphetamine and cocaine produces reward is by activating the reward mechanisms just discussed in the orbitofrontal cortex (Phillips, Mora and Rolls 1981, Voellm, De Araujo, Cowen, Rolls, Kringelbach, Smith, Jezzard, Heal and Matthews 2004), and regions to which it projects such as the nucleus accumbens (Phillips, Blaha and Fibiger 1989, Phillips and Fibiger 1990).

7.5.3 Amygdala

Self-stimulation pulses applied to the monkey amygdala activate lateral hypothalamic and orbitofrontal cortex neurons also activated by the taste, sight or smell of food (Rolls 1976a, Rolls, Burton and Mora 1980c). This is one explanation of why electrical stimulation of the amygdala can produce reward.

Another, consistent, explanation is that neurons in the amygdala can be activated by the taste of food, or by the sight of food (Sanghera, Rolls and Roper-Hall 1979, Ono, Nishino,

Sasaki, Fukuda and Muramoto 1980, Rolls 2000d, Nishijo, Ono and Nishino 1988, Wilson and Rolls 1993, Scott, Karadi, Oomura, Nishino, Plata-Salaman, Lenard, Giza and Aou 1993, Kadohisa, Rolls and Verhagen 2005b, Wilson and Rolls 2005).

The underlying conceptual reason though for an involvement of activation of amygdala neurons in brain-stimulation reward is that the amygdala is a region, evolutionarily old, implicated in stimulus–reward association learning (see Chapter 4). For its output to be interpreted as a secondary reinforcer, some part of the output of the amygdala must be interpretable by the rest of the brain as being positively reinforcing; and for the amygdala to play a role in such pattern association learning, the primary reward (e.g. the taste of food) must be represented in the amygdala. Electrical stimulation of the amygdala could also tap into this representation of primary reward. In addition, electrical stimulation of the amygdala may produce reward because it taps into systems concerned more generally with rewards, including those produced by facial expression (see Chapter 4).

7.5.4 Nucleus accumbens

The nucleus accumbens is a self-stimulation site in primates and rats (Rolls 1971b, Rolls 1974, Rolls, Burton and Mora 1980c). The rewarding electrical stimulation here produces activation of neurons in the lateral hypothalamus and orbitofrontal cortex also activated by the sight and taste of food (Rolls, Burton and Mora 1980c). This may be a sufficient explanation for self-stimulation of the nucleus accumbens.

However, a more conceptual explanation is as follows. The accumbens may be a system through which conditioned incentives (secondary reinforcers) learned about in the orbitofrontal cortex and amygdala are connected to influence instrumental action. In particular, although the nucleus accumbens is not involved in action–outcome learning itself, it does allow the affective states retrieved by the basolateral amygdala (BLA) to conditioned stimuli to influence instrumental behaviour by for example Pavlovian-instrumental transfer, and facilitating locomotor approach to food which appears to be in rats a Pavlovian process (Cardinal et al. 2002). Such a role in for example processing a signal that facilitates approach would imply that the animal would work to obtain electrical stimulation of the output, which has to be interpretable as being rewarding if the secondary reinforcing properties of stimuli are to be interpreted by this route by the rest of the brain.

It may be that, because dopamine inputs to this region enhance the secondary reinforcing properties of incentive stimuli (Cador, Robbins and Everitt 1989, Everitt and Robbins 1992) [17], presumably by facilitating transmission through the nucleus accumbens, psychomotor stimulants such as amphetamine and cocaine come to produce their rewarding properties (see Section 8.3). Moreover, brain-stimulation reward of some sites such as the ventral tegmental area where dopamine cell bodies are located occurs because of activation of nucleus accumbens neurons through the dopaminergic ascending connections (see Section 8.3).

7.5.5 Central gray of the midbrain

Electrical stimulation of some regions of the brain can lead to analgesia in animals ranging from rats to humans and can be equivalent in its pain-reducing properties to large doses of morphine (Liebeskind and Paul 1977). These analgesic effects can last for hours after only

[17] They showed that amphetamine injections into the nucleus accumbens enhanced the reinforcing properties of conditioned incentive stimuli.

seconds of stimulation. The analgesia is often for only part of the body, so that a strong pinch to one side but not to the other might be ignored. This shows that the stimulation-produced analgesia is not simply some general interference with the animal's ability to respond to stimulation.

The effective stimulation sites are in the medial brainstem, and extend from the rostral medulla (nucleus raphe magnus), through the midbrain central grey matter, towards the hypothalamus. There is no clear relation with brain-stimulation reward mechanisms, because at some sites analgesia and self-stimulation are found and at others the stimulation is aversive but is followed by analgesia (Koob and Le Moal 1997).

It has been shown that naloxone, a specific morphine antagonist, reverses, at least partly, stimulation-produced analgesia in both the rat and humans (Akil, Mayer and Liebeskind 1976, Adams 1976). The endogenous morphine-like peptide enkephalin (Hughes 1975, Hughes, Smith, Kosterlitz, Fothergill, Morgan and Morris 1975, Cooper et al. 2003) injected intraventricularly yields analgesia (Beluzzi, Grant, Garsky, Sarantakis, Wise and Stein 1976), and central grey matter stimulation releases this substance or a peptide similar to it (Liebeskind, Giesler and Urca 1985). Further, there are stereospecific opiate-binding sites in the central grey matter, and elsewhere in the brain (Kuhar, Pert and Snyder 1973). These findings raise the possibility that stimulation-produced analgesia is effective because it causes the release of a naturally occurring morphine-like substance which acts on opiate receptors in the central grey matter and elsewhere to induce analgesia.

The stimulation at these brainstem sites may be rewarding because of activation of enkephalin-containing neurons which make synapses on to the dopamine neurons in the ventral tegmental area (Phillips and Fibiger 1989). The central gray stimulation may be rewarding because it is part of an endogenous opiate-containing system that controls the threshold for pain, which in emergency situations might be elevated, presumably to avoid being disabled by severe pain in situations that threaten survival.

7.6 Some of the properties of brain-stimulation reward

There are several properties of brain-stimulation reward that seemed surprising when they were discovered. However, by understanding these properties of brain-stimulation reward, we come to see that these are also properties of natural rewards, and we thus enhance our understanding of some of the properties of natural rewards.

7.6.1 Lack of satiety with brain-stimulation reward

One of the most striking properties of brain-stimulation reward is its persistence and lack of satiety. A record of a rat working for brain-stimulation reward for 24 h essentially without stopping is shown in Fig. 7.6. At the time that this was first discovered (see, e.g., Olds (1958)) it seemed quite extraordinary, because normally we do not work for a reward for that long. With eating, for example, we like the taste of food but during the course of a meal its reward value drops to zero, and we no longer work for it. The folk psychology was that reward somehow produced satiety, so we never worked for a reward for long. But the evidence from brain-stimulation reward showed that reward per se does not produce satiety.

This finding was useful, because it led to reconsideration of what happens with food reward (see Rolls (1975)), which does not, of course, itself produce satiety either, as the sham

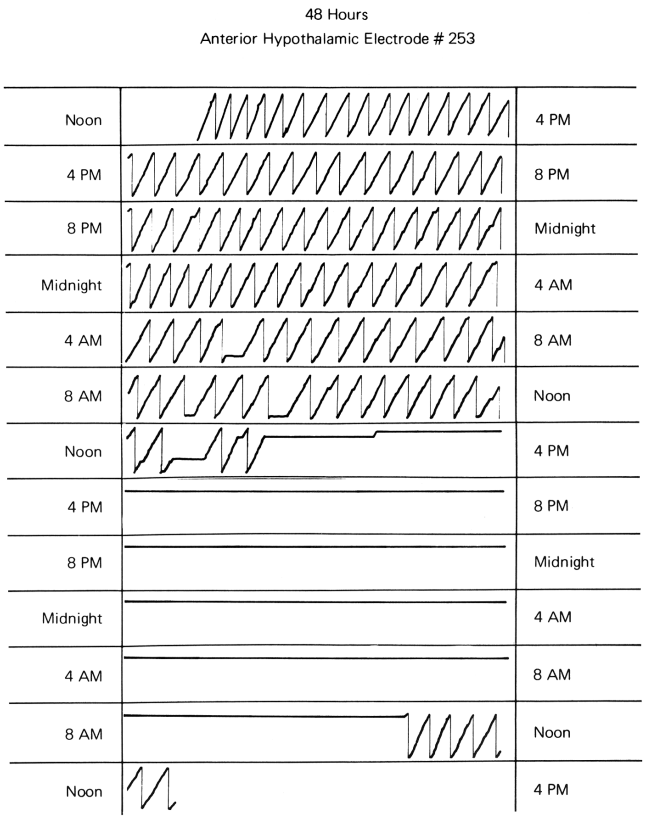

Fig. 7.6 This cumulative record shows that intracranial self-stimulation can be very vigorous and persistent. Each time the rat bar-pressed (for a 0.5-s train of electrical stimulation) the pen stepped once vertically. After 500 steps, it resets to 0. A four-hour time period is shown along the horizontal axis. (From J. Olds 1958.)

feeding experiments described in Section 5.2 show very clearly. The point with respect to feeding is that normally when food accumulates in the stomach and intestine it does produce peripheral satiety signals, and via these brain mechanisms reduces the reward value of sensory stimulation produced by the sight, smell, and taste of food, as shown in Chapter 5. But there is little about food reward per se that produces satiety. The only respect in which giving food reward does affect satiety is that there is some sensory-specific satiety, which, as described in Chapter 5, is sufficient to produce variety effects in food reward, but is not sufficient to reduce food reward to zero, and stop feeding (as shown by the continuing feeding in the sham feeding preparation). So the finding of little satiety produced by brain-stimulation reward is actually in line with other rewards, and the persistence of brain-stimulation reward helped to underline this. It is just that normally when we have a food or water reward, we ingest the food or water, and thereby close the loop and produce negative feedback to reduce the reward value of the food. As discussed in Chapter 9, there may be special mechanisms to turn off the rewards associated with sexual behaviour in males just after ejaculation.

The conclusion is that in general reward itself does not produce satiety, apart from some

sensory-specific satiety to help behaviour to switch after some time to another reward, and there are special mechanisms usually associated with the rewarded behaviour (such as the ingestion of food) that act to neurally turn off the reward.

7.6.2 Rapid extinction

Extinction from self-stimulation can be very rapid (Seward, Uyeda and Olds 1959) even when the manipulandum is withdrawn, so that non-rewarded responses are prevented (Howarth and Deutsch 1962).

A factor that determines the number of responses in extinction is the time elapsed since the last reward (Howarth and Deutsch 1962), which was not found to apply for thirsty rats trained for water, that is where there is a string relevant drive (Quartermain and Webster 1968).

Perhaps the major factor that accounts for the rapid extinction of self-stimulation often reported is that no relevant drive is present. If rats are hungry, extinction from brain-stimulation reward is very prolonged (Deutsch and Di Cara 1967). Thus one conclusion that can be made from studies with brain-stimulation reward is that resistance to extinction depends on the presence of an appropriate drive.

The role of a relevant drive in the rapidity of extinction was demonstrated for conventional reinforcers by Panksepp and Trowill (1967b), who found a trend towards rapid extinction in satiated rats previously rewarded with chocolate milk.

Another factor that contributes to rapid extinction is the short time between pressing the manipulandum and receiving brain-stimulation reward, in contrast to the one or two seconds delay between pressing a manipulandum and then finding food or water reward available in a cup (Gibson, Reid, Sakai and Porter 1965, Panksepp and Trowill 1967a). Keesey (1964) also found that errors in learning a brightness discrimination are increased when the brain-stimulation reward is delayed.

This conclusion is relevant to interpreting investigations relevant to animal welfare. Although an animal may work for a reward, if it shows rapid extinction when the reward is no longer available, this could be because there is little motivation for that particular reward.

7.6.3 Priming

Rats will run along a runway to obtain electrical stimulation at the end of the runway. If some of the electrical stimulation is given in addition at the start of the runway, then the rats will run faster (Gallistel 1969). The stimulation given at the start of the runway is said to have a priming effect, which decays gradually (see Fig. 7.7 – the priming effect decayed over a particularly long time in this rat). Priming stimulation (given by the experimenter) can also cause a rat to return to a self-stimulation lever and start self-stimulating. This may be useful if the rat does not bar-press at once when it is put in a self-stimulation box, i.e. if it shows an ‘overnight decrement effect’.

One factor that may contribute to the priming effect is arousal. It has been shown that arousal, measured by EEG (electroencephalogram) desynchronization and by increased locomotor activity, is produced by stimulation of reward sites along the medial forebrain bundle (MFB) (Rolls 1971c, Rolls 1971b, Rolls 1975, Rolls and Kelly 1972). This arousal decays in a very similar way to the priming effect, as shown, for example, in Fig. 7.7. The arousal must at least influence medial forebrain bundle (MFB) self-stimulation. Because of its similarities to the priming effect, it may well mediate the priming effect, at least in part. Similarities

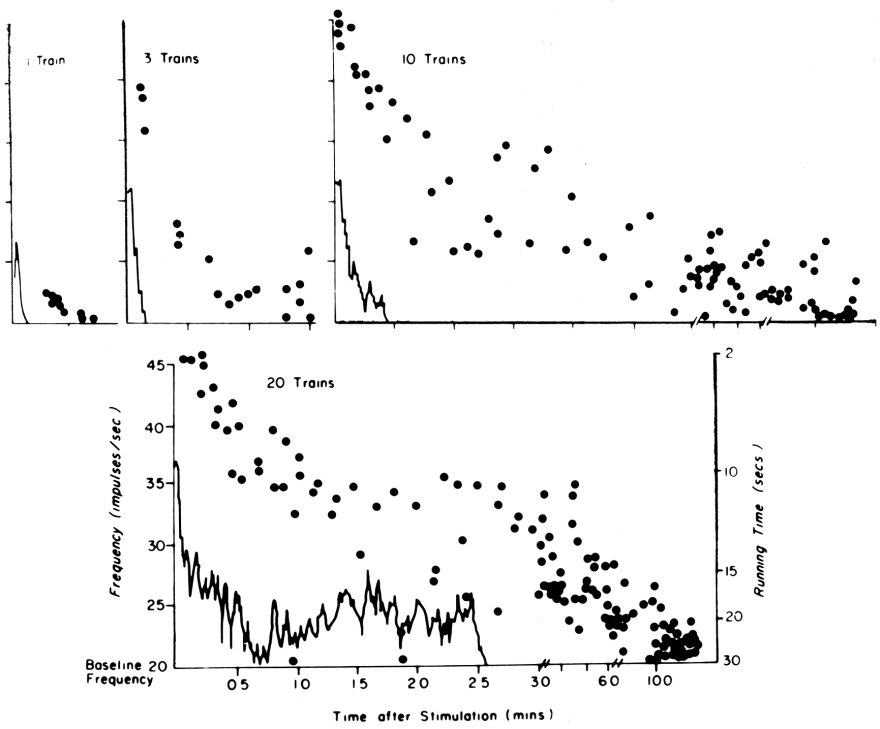

Fig. 7.7 The priming effect of brain-stimulation reward. Running speed (closed circles) for brain-stimulation reward as a function of time after different numbers of priming trains of stimulation given before the first trial (after Gallistel 1969). The firing rate (continuous line) of a neuron in the reticular activating system of the midbrain as a function of time after different numbers of trains of stimulation delivered at a lateral hypothalamic self-stimulation site is shown for comparison (after Rolls 1971a–c, 1975).

include the temporal nature of the decay, the greater magnitudes and durations of the effects produced by more stimulation trains (see Fig. 7.7), and the refractory periods of the neurons through which the effects are produced (Rolls 1971c, Rolls 1971a, Rolls 1974). Arousal may contribute not only to priming effects, but also to differences between some self-stimulation sites. For example, arousal is elicited by rewarding stimulation of MFB, but not nucleus accumbens, sites, and differences between these sites include hyperactivity and fast rates of self-stimulation at MFB self-stimulation sites (Rolls 1971b, Rolls 1974, Rolls 1975).

A second factor that may contribute to priming effects is incentive motivation, that is the motivation that can be produced by giving a reward. For example, if satiated animals are primed with an intraoral reward of chocolate milk, then they will resume bar-pressing to obtain more chocolate milk (Panksepp and Trowill 1967b). It is important that this effect is seen most markedly under zero-drive conditions, e.g. when an animal is neither hungry nor thirsty. These are the conditions under which self-stimulation experiments are often run. Incentive motivation is seen in other situations with natural reward, e.g. as the salted-nut phenomenon (Hebb 1949), and as the increase in the rate of ingestion seen at the start of a meal (LeMagnen 1971) (see Sections 3.3, 4.6.1.2 and 5.3.1).

This second factor may be relevant to investigations in animal welfare, in which it may

be found that animals will work to obtain certain rewards if they have just been given or shown them, but do not appear to rank these rewards highly when they are pitted in long-term preference tests against more important rewards, such as those relevant to internal homeostatic states such as hunger and thirst (Dawkins 1990, Mason, Cooper and Clareborough 2001). Such rewards may be acting as low priority rewards, which are chosen temporarily after they have been presented due to incentive motivational effects. Care must thus be used in the design of preference tests in animals when these are used to provide evidence about the priority the animals give to different reinforcers, to ensure that such priming or incentive motivational effects are adequately controlled for. In addition, care must be taken that the animal is choosing a stimulus or condition as a goal, and is not just acting out of habit. As shown in Section 4.6.1.2, overtraining can lead to behaviour being controlled by stimulus–response associations or habits, and the value of the goal may not be taken into account in behavioural tests if they are run under habit as compared to instrumental goal value conditions, as shown for example by reward devaluation experiments.

A third factor that may contribute to priming effects is conflict. Kent and Grossman (1969) showed that only some rats needed priming after an interval in which self-stimulation was prevented by withdrawal of the lever. In the 'primer' rats the stimulation seemed to produce reward and aversion in that self-stimulation was accompanied by squeaking and defecation. It was suggested that during the time away from the bar the reward decayed more rapidly than the aversion, so that self-stimulation was not resumed without priming. It was also found that 'non-primer' rats could be converted into 'primers' by pairing painful tail shock with the brain-stimulation reward. Although Kent and Grossman (1969) labelled one group of their rats as 'non-primers', a priming effect can be demonstrated in this type of animal using, for example, a runway (Reid, Hunsicker, Kent, Lindsay and Gallistel 1973).

Thus there are several explanations of the priming effect which are not necessarily contradictory and which may all contribute to the priming effect.

7.7 Stimulus-bound motivational behaviour

Electrical stimulation at some brain sites can elicit feeding, drinking and other consummatory types of behaviour (Valenstein, Cox and Kakolewski 1970). The behaviour may be called 'stimulation-bound' because it occurs during the electrical stimulation, or 'stimulus-bound' because the behaviour is associated with a particular goal object, for example food pellets. If small-tipped stimulation electrodes are used relatively specific behaviours are elicited, such as drinking with electrodes near the zona incerta, and feeding with electrodes in the lateral hypothalamus (Olds, Allan and Briese 1971, Huang and Mogenson 1972).

A frequently observed feature of such behaviour is plasticity, that is stimulus-bound feeding can develop into stimulus-bound drinking if food is removed from the environment and replaced with water (Valenstein et al. 1970). It is as if the stimulation activates the animal and the behaviour that is elicited depends on which environmental stimuli are available for the animal to respond to, for example, food to chew or water to lap. This type of interpretation receives support from the observation that a mild continuous tail-pinch (with, for example, a paper clip) leads to 'stimulus-bound' types of behaviour such as eating in the rat (Antelman and Szechtman 1975). Because of such findings, it is difficult to interpret stimulus-bound behaviour produced by brain stimulation as a proof of activation of a hunger or thirst mechanism — rather it could be a more general type of behavioural activation.

It is worth noting that although stimulus-bound behaviour may not represent activation of a specific drive (e.g. hunger), there is evidence that reward elicited by electrical stimulation can be relatively specific. For example, it may be equivalent to food for a hungry animal or water for a thirsty animal (see Section 7.2).

7.8 Conclusions

Animals, including humans, will learn to stimulate electrically certain areas of the brain. At some sites the stimulation may be equivalent to a natural reward such as food for a hungry animal, in that hunger increases working for brain-stimulation reward at these (but not at other) sites.

It has been found in the monkey that one population of neurons activated by the brain-stimulation reward at these sites is in the region of the lateral hypothalamus and substantia innominata. Some of these neurons are also activated by the sight and/or taste of food if the monkey is hungry, that is when the food is rewarding. The latency of the responses of these neurons to the sight of food is 150–200 ms. This is longer than the responses of sensory neurons to visual stimuli in the inferotemporal cortex and dorsolateral amygdala, but shorter than the latency of the animal's behavioural responses to the sight of food, as shown by electrographic recording of the muscles that implement the motor responses. Thus it is possible that these hypothalamic neurons mediate some of the reactions of the hungry animal to food reward, such as the initiation of feeding and/or autonomic and endocrine responses.

In a comparable way, brain-stimulation reward of the primate orbitofrontal cortex occurs because it is activating systems normally concerned with decoding and representing taste, olfactory, tactile and visual rewards.

In this way reward-related processes can be identified and studied by analysing the operations (from sensory input through central control processes to motor output) that are involved in the responses of animals to rewarding stimuli.

Self-stimulation of some sites may occur because neurons whose activity is associated with food reward are activated by stimulation at these sites.

At other sites, brain-stimulation reward may be produced because the stimulation mimics other types of natural reward such as, in the nucleus accumbens, the effects of secondary reinforcers.

At other sites, as shown by verbal reports in humans, the electrical stimulation is rewarding because it is producing mood states such as a feeling of happiness normally produced by emotional stimuli.

The findings with brain-stimulation reward are helpful, because they provide additional evidence about whether a particular part of the brain is involved in reward processes. Consistent with this point, in general, brain-stimulation reward does not occur in brain areas involved in early sensory processing (e.g. in visual cortical areas up to and including the inferior temporal visual cortex), where on independent grounds it is believed that in primates the reward value of stimuli is not represented (see Chapter 4). Nor does brain-stimulation reward occur in general in motor structures such as the globus pallidus (see Fig. 7.5), nor in motor cortical areas (see Rolls (1974) and Rolls (1975)). Thus the evidence from brain-stimulation reward complements the other evidence described in this book that it is at special stages of the pathways that lead from sensory input to motor output that reward is represented, and that this is part of brain design (see further Chapters 2–11).

Brain-stimulation reward also historically helped to draw attention to important points, such as the fact that reward per se does not produce satiety (Section 7.6.1); that the time between the operant response and the delivery of the reward (or a stimulus associated with the reward) has important implications for what happens when the reward is no longer available (Section 7.6.2); and that effects such as rapid extinction, and priming, are found under low-drive conditions, that is, when the motivation for the reward is low (Sections 7.6.2 and 7.6.3).

7.9 Apostasis

[18] There was a great deal of research on electrical brain-stimulation reward in the years after its discovery (reported by Olds and Milner (1954)) until 1980. After that, research on brain-stimulation reward tailed off. Why was this? I think that one reason was that by the middle 1970s it was becoming possible to study reward mechanisms in the brain directly, by recording from single neurons, in order to provide a fundamental understanding of how natural rewards are being processed by the brain (see Rolls (1974), Rolls (1975), Rolls (1999a), and this book). This led to the analysis of the neural mechanisms involved in the sensory processing, and eventually to an understanding of the decoding of the reward value, in the taste, olfactory, visual, and touch systems of primates. In the case of visual processing, this involved investigating the learning mechanisms that enable visual stimuli to be decoded as rewarding based on pattern-association learning between visual stimuli and primary reinforcers such as taste (see Rolls and Treves (1998), Rolls and Deco (2002), and Appendix 1). By analysing such sensory information processing, an explanation for why electrical stimulation of some parts of the brain could produce reward became evident.

At the same time, the investigations of brain-stimulation reward were very helpful, because they provided additional evidence that neurons putatively involved in reward because of the nature of their responses (e.g. hypothalamic, orbitofrontal cortex, or amygdala neurons responding to the sight, smell, or taste of food) were actually involved in food reward, because electrical stimulation which activated these neurons could produce reward (see Rolls (1975), Rolls (1999a), and Chapters 4–6).

In a comparable way, electrical brain-stimulation reward was also of significance because it pointed the way towards brain regions such as the ventral tegmental area dopamine neurons, which, via their projections to the nucleus accumbens, can influence brain processing normally involved in decoding by the amygdala and orbitofrontal cortex environmental stimuli as being rewarding, and enabling these signals to influence behaviour (see Section 8.4.3.1). The relation of this brain dopamine system to reward led eventually to the discoveries that this dopamine neural system, and its projections to the orbitofrontal cortex, are involved in the rewarding and indeed addictive properties of drugs of abuse such as amphetamine and cocaine (Phillips, Mora and Rolls 1981, Phillips and Fibiger 1989, Koob and Le Moal 1997) (see Section 8.3).

A second reason why research on electrical brain-stimulation reward decreased after about 1980 is that it then became possible to study the pharmacological substrates of reward not only by investigating how pharmacological agents affect electrical brain-stimulation reward, which required very careful controls to show that the drugs did not affect rewarded behaviour

[18] Apostasis, from the Greek, meaning standing apart or away from; hence a meta-statement (literally an 'about' statement) or a comment. Different from the Latin p.s. (postscriptum translated as post script) which means written after.

just because of motor or arousal side effects (see Section 8.3), but also by investigating directly the self-administration of pharmacological agents, both systemically and even directly to the brain (e.g. Phillips, Mora and Rolls (1981)). The results of these investigations, described in Section 8.3, taken together with the increasing understanding of brain mechanisms involved in natural reward processing and learning (see Chapters 4–6), led directly to rapid advances in understanding the processing in the neural systems that provides the neural basis of the self-administration of drugs (see Section 8.3).

Brain-stimulation reward, though less investigated today, does nevertheless provide a way to present repeatedly for hours on end a reward that does not satiate. Indeed, the persistence of responding to obtain brain-stimulation reward was one of the startling facts that led to the clear exposition of how reward and satiety signals are very distinct in their sensory origin, and how motivational signals such as hunger and thirst actually modulate the reward value of sensory input produced, for example, by the taste of food (see Chapter 5). Studies with brain-stimulation reward emphasized the fact that (apart from some sensory-specific satiety), the delivery of reward per se does not produce satiety.

The discoveries with brain-stimulation reward also led to advances in understanding behaviour under low-drive conditions, including priming effects and rapid extinction, and this understanding is relevant to interpreting modern studies in animal welfare.