List of appendices

Appendix 2

The periaqueductal grey, medial hypothalamus, and amygdala

A2.1 Introduction

This appendix is to a large extent an expansion of parts of Chapter 6. Some parts of it are taken verbatim from Chapter 6 and are included here for completeness of the arguments.

Our analysis in Chapters 1–5 led us to a distinction between pure fear and anxiety. In pure fear, defence is simple and requires only escape or active avoidance controlled by the fight/flight/freeze system (FFFS). In anxiety, defence is more complicated and fear is compounded with a tendency to approach the source of potential threat—producing an approach–avoidance conflict. In anxiety, the output of the FFFS (as well as appetitive responses controlled by the behavioural approach system, BAS) must be inhibited so that defence is based on active risk analysis controlled by the behavioural inhibition system (BIS). This implies a hierarchical organization, with anxiety systems providing an extra, inhibitory, layer superimposed upon pure fear systems. It seems likely, therefore, that the neurology of fear will be bound up in the neurology of anxiety. However, a further complication of anxiety is that the avoidance component of the approach–avoidance conflict need not involve fear. We concluded that frustration and other affectively negative states can also produce anxiety. However, fear is clearly a logical precursor to at least some types of anxiety and so we will analyse its neurology here before we attempt to analyse the neurology of anxiety. Luckily, the neurology of primary defence systems has been worked out in considerable detail and, it turns out, the higher levels of the system control not only fear but also frustration.

The tight linkage between fear and anxiety, as well as the potential complexity of fear-related systems, is shown by the fact that simple classical conditioning of fear to contextual cues produces noticeable reactions in much of the allocortex, isocortex, subcortical telencephalon, thalamus, hypothalamus, and many areas of the brain stem; and, in the majority of these areas, peripheral administration of diazepam reduces (but does not eliminate) the reaction (Beck and Fibiger 1995). Interestingly, the central nucleus of the amygdala is the only place in which these authors observed an increase in activity with diazepam.

We can restrict ourselves to a single appendix devoted to the primary defence system for two reasons. First, in the key area of the amygdala, there have recently appeared a number of excellent reviews (Davis 1992*a*; Aggleton 1993; Le Doux 1994, 1995) as well as a volume edited by Aggleton (1992; see also Le Doux 1996 for an amygdalo-centric view of emotions in general) on which we can and will draw heavily. Second, while there are controversies about precise details, there is broad agreement about the general organization of the defence system (leaving aside the hippocampal contribution). We feel, therefore, that we can present a brief summary of what is, largely, a consensus view of the primary defence system and refer to the relevant reviews for the extensive analysis on which it is based.

A2.2 The periaqueductal grey, fight, flight, and freezing

For the purposes of this book we will treat the periaqueductal grey (PAG) as the lowest level of the defence system. Although the PAG is far from homogeneous (see, for example, Zhang *et al.* 1990; Fig. 1 in Herbert and Saper 1992; and reviews by Shipley *et al*. 1991; Carrive 1993; and Bandler and Shipley 1994), we can characterize its business as 'integrated responding to noxious stimulation' (Liebman *et al.* 1970, p. 353) and, in particular, the release (McNaughton 1989, Chapter 2) of fight, flight, and freezing (Blanchard *et al*. 1981). In this sense, activity in the PAG can be viewed as providing a signal 'here is a proximal threat'—but this is a special kind of signal which is simultaneously an imperative to action. This combination of stimulus and response features makes it more convenient to use the term 'goal' (which combines both stimulus and response aspects) to describe the activity—specifically activity in the PAG implies that the animal is seeking the goal of immediate safety. However, to describe the PAG in this way is to imply that it is not only the lowest level of an integrated defence control system, but also one of the higher levels of more specialized systems which deal with the specific details of each of the fight, flight, freezing, autonomic, and vocalization responses which can result (e.g. Holstege 1989; Carrive and Bandler 1991; Lovick 1993; Jurgens 1994). Here we will argue that input to the PAG can release a tonic inhibition of each of these separate systems and there must be additional inputs which release (or activate) the specific observed behaviour at any point in time—with an implied competitive interaction between them. At least in the case of conditioned freezing, it appears that it may only be the behavioural response which is controlled by the PAG and that the autonomic response is controlled by the lateral hypothalamus (Le Doux *et al*. 1988, see also next section). Some part of the discrimination of defensive distance which would determine the precise outputs required may be provided by inputs from areas such as the superior colliculus (Redgrave and Dean 1991).

As reviewed by Graeff (1994; but see also Bandler and Shipley 1994), the neural substrate for freezing could be the ventral periaqueductal grey and this would include conditioned freezing (M. Kim *et al.* 1993). The PAG is also a crucial area for the production of fight/flight responses since its chemical activation (which avoids the problems of non-specificity of electrical stimulation) elicits fight/flight while its lesion blocks the capacity of stimulation of the medial hypothalamus or amygdala to produce fight/flight.

Stimulation of the PAG also elicits a similar pattern of responses to that seen in close proximity to a predator—an alternation between periods of intense freezing and explosive, undirected running and vertical jumping (undirected escape). This could be the result of a simultaneous, non-physiological, activation of quite independent, but anatomically adjacent, pathways. However, the similarity to the pattern seen in response to a predator suggests that the PAG stimulation is releasing behaviour in an equivalent fashion to the natural stimulus. The absence of attack in this case can be attributed to the lack of a suitable object.[1] Certainly, with high levels of activation and a suitable object to attack 'all of the behavioural signs of defence, including directed attack, are found within the PAG' (Bandler and Carrive 1988).

Graeff equates activity in the PAG with panic reactions in humans—an issue to which we will return when considering ascending 5-HT systems (Appendix 10; for a somewhat different neurology see Gorman *et al*. 1989). It should be noted that 'proximal threat' should here be interpreted broadly since the 'fight or flight reaction also occurs in response to non-

painful tactile stimulation applied to the dorsum or vibrissae, [and] an even more vigorous response is elicited by acute pain inflicted from the outside, or *asphyxia'* (Graeff 1994, p. 813, our emphasis). Even 'proximal threat' in its most general form may not encompass all PAG activity since lesions to PAG impair passive avoidance and increase ambulation and decrease defecation in the open field (Liebman *et al*. 1970), while glycine antagonists, or propranolol, injected into the dorsal PAG (DPAG) have 'anxiolytic' effects in the plus maze (Audi *et al.* 1991; Matheus *et al*. 1994). It may be best to view it, therefore, as the primordial substrate for fear. Its behavioural functions seem broad enough to be so characterized and, certainly, it is the lowest point in the descending defence system which could be assigned so broad a function. A more general involvement in fear could also be supported by its projections to areas such as the amygdala. For certain types of stimuli, therefore, the DPAG would be the primary receiving area and could both instantly initiate evasive action and pass the fact of detection of the information on to areas concerned with anticipation, and hence avoidance, of those stimuli in future.

It is consistent with this general view, and our previous separation of fear from anxiety, that injection of benzodiazepines into the PAG does not affect passive avoidance. However, benzodiazepine injections into the PAG do affect conditioned hypoalgesia (Harris and Westbrook 1995; see also Helmstetter and Tershner 1994) and so the PAG may be the direct target through which at least these types of anxiolytic drugs produce some of their actions. It also appears to be an important relay through which areas such as the amygdala can modify startle responses (Fendt *et al.* 1994) and defensive threat (Shaikh *et al.* 1994), although it does not appear to be involved in conditioned changes in blood pressure (Helmstetter and Tershner 1994). At least some of these effects may be mediated by opioidergic synapses (Da Costa *et al.* 1995). Likewise, 'since important excitatory amino acid (EAA) projections from the dorsomedial and ventromedial hypothalamus to the midbrain central grey have been demonstrated, it is suggested that descending EAA containing nerve fibres from the medial hypothalamus project to NMDA [*N*-methyl-d-aspartate] receptors in the DPAG and play an important role in the mediation of aversive–defensive behaviour . . . Because electrical or chemical stimulation of DPAG induces behavioural changes that markedly resemble a panic attack in both experimental animals and in man, it has been suggested that the anti-panic effect of drugs would be due to inhibition of neurons in the DPAG' (Matheus *et al*. 1994, p. 568; see also Jenck *et al*. 1995; for direct evidence of the role of NMDA receptors see Schubert *et al*. 1996).

Although we will not go into it here, it should be noted that not only is the PAG divided into a number of functionally discrete areas (e.g. Holstege 1989; Zhang *et al.* 1990; Carrive *et al*. 1997), but many of these areas may be topographically organized both with respect to, for example, visceral targets (Carrive and Bandler 1991) and with respect to their connections to and from rostral areas such as the central nucleus of the amygdala (Rizvia *et al*. 1991) and prefrontal cortex (Shipley *et al*. 1991) and caudal areas such as the A1 noradrenergic group of the ventrolateral medulla (Herbert and Saper 1992). Likewise, in its relations to the hypothalamus the PAG is clearly not the only executive target of hypothalamic outflow (e.g. van Erp *et al*. 1993). For a detailed review of all of these issues see Carrive (1993). It should also be noted that the inferior colliculus shows very similar properties to the PAG and may activate escape mechanisms independently of the PAG (see review by Brandão *et al.* 1993). Although adding detail and some complexity to the story, none of these facts changes the fundamental picture which we have painted of the PAG.

The majority of the efferents from the PAG are descending and will be ignored here as simply providing detailed control of the different behavioural outputs controlled by the PAG. There are ascending (e.g. nociceptive) inputs to PAG, which are consistent with a fundamental (and phylogenetically old) role in the most basic defensive behaviour. However, there are also a mass of descending inputs 'from medial frontal cortex (infralimbic, prelimbic, anterior cingulate, precentral medial cortex) and from lateral cortex (anterior insular, posterior insular, perirhinal cortex) . . . from amygdala, bed nucleus of the stria terminalis, basal telencephalon and hypothalamus' (Carrive 1993; see also Bragin *et al*. 1984), particularly the medial hypothalamus as we have mentioned already.

The telencephalic connections open the way for cognitively very complex events to engender panic. However, it should be noted that the descending input from the amygdala appears to control situation-induced analgesia not only to cat exposure and stimuli which predict shock (which could be classed as 'cognitively complex') but also to acute footshock (Fox and Sorenson 1994). Nonetheless, the simplest and most direct inputs are those from subcortical areas which indicate current tissue damage (e.g. pain, asphyxia). It is noteworthy, therefore, that the hippocampal formation has no direct inputs to the PAG, but has direct inputs to virtually all the higher areas which project to it.

This absence of hippocampal input is logical if, as we shall suggest later, the hippocampus can inhibit active avoidance reactions when they are inappropriate. The lack of hippocampal input to the PAG, or to the sources of ascending input to the PAG, is attributable to the fact that behavioural inhibition and risk analysis would never be appropriate once tissue damage is actually occurring. At this point the only appropriate response is fight or flight. One complication to this picture is that the PAG appears to be a relay in the pathway controlling fear-potentiation of the startle response, without being involved in the control of startle itself (Fendt *et al*. 1996); we will discuss this further in the section on the startle response.

A2.3 The medial hypothalamus and escape

Of the various descending inputs to the PAG, that from the medial hypothalamus (MH) appears most closely related in function to the immediate outputs of the PAG. Certainly there are tight anatomical connections between the two areas and, for example, 'all parts of the VMH [ventromedial hypothalamus] send a massive topographically organized projection to the periaqueductal grey' (Canteras *et al.* 1994, p. 41). As we will see, the functions of the medial hypothalamus appear very similar to those of the PAG, but with some critical differences which we will argue are due to the higher level ('slow and sophisticated' as opposed to 'quick and dirty') of the organization of escape by the MH.

This 'motor' role for the MH might appear strange in the context of the strong 'visceral' role of the hypothalamus in general, which has been known in some detail for many years (see, for example, review by Fulton 1932). However, if we see this visceral role as the result of coordination of responses to stimuli which will require very vigorous action, 'those adjustments essential for escape and combat' (Fulton 1932, p. 20) , then it is not surprising that part of the hypothalamus should also coordinate at least some of the behavioural as well as autonomic components of these reactions, since the critical inputs required to elicit the behavioural and autonomic responses will be quite similar, provided the motor output is controlled in a fairly simple manner. There is also reason to see the dorsomedial hypothalamus (DMH) as being particularly involved in responses to acute stress (e.g. DiMicco and Monroe 1996; DiMicco *et al*. 1996).[2]

By contrast to the undirected, explosive escape elicited by PAG stimulation, chemical activation of the medial hypothalamus produces directed escape (see Graeff 1994; Silveira *et al.* 1995; note that kainate rather than glutamate must be used to achieve these effects, Silveira and Graeff 1992). This escape is distinguished by a lack of the upright jumping seen with PAG stimulation and by its occasional interruption by prolonged rearing (Silveira and Graeff 1992). (C-fos and lesion data suggest that the dorsal premammillary nucleus may be particularly important for the control of freezing and escape responses to a predator; Cantera *et al*. 1997).There are reciprocal connections between the PAG and the MH, but lesion of the PAG blocks the escape produced by MH stimulation whereas the reverse is not the case. This suggests a picture of the motor control of threat analogous to that presented in Fig. 6.1 for the perceptual analysis of threat: the PAG, by itself, can produce a prototypical, 'fuzzy' escape response (homologous to the fuzzy perceptual picture provided by the thalamus) and the MH superimposes on this response increased perceptual precision and direction (homologous to the increased perceptual precision provided by visual cortex). Although Graeff does not suggest this, it seems likely that extreme levels of activation of the MH would have a net effect equivalent to simple PAG stimulation, as a result of a loss of coordination at high intensities. This idea of a downward cascade of activation at high levels of intensity is important for our treatment of the relationship between high levels of anxiety and the occurrence of panic (Chapter 11).

Shekhar (1994) makes an explicit link between activation of the dorsomedial hypothalamic 'cardiostimulatory area' by GABA blockade (see also Gören *et al*. 1996) and panic disorder. GABA blockade 'elicits not only increases in heart rate, blood pressure and respiratory rate but also 'escape'-oriented locomotion, a selective enhancement of 'fear' or 'avoidance' responding and an increase in experimental anxiety as measured in the 'conflict' (punishment-induced suppression of lever presses for sweetened milk), elevated plus-maze and social interaction tests . . . increases in plasma catecholamines, plasma adrenocorticotropic hormone and plasma corticosterone' (Shekhar 1994, p. 748; see also Shekhar 1993; Narita *et al*. 1994). Whether or not DMH is the site at which primary panic originates (or whether, like telencephalic areas, it is simply a source of PAG activation) it is clear that pathology of the DMH could lead to panic in humans.

There is one way in which the MH and the PAG are diametrically different. Activation of the MH (or the lateral septum, a fact we will return to in Appendix 7) reduces defensive aggression in animals (which can be equated with the bulk of aggression in humans) while lesions increase aggression (see Albert *et al.* 1993). This is the opposite effect to that which would be obtained with the PAG[3] and, despite their otherwise similar effects, is what we would expect in a hierarchically organized system. We have argued that the PAG is associated with explosive, disorganized escape. In such escape, the animal could easily head in the direction of the predator and this would require attack. By contrast, if the DMH is associated with organized escape then any tendency to attack the predator could interfere with escape, with potentially disastrous consequences.

The opposite relations of the MH and the PAG to aggression (which is consistent with the idea of levels of defence) also fits with the fact that neither the medial nor the lateral hypothalamus appears to be involved in the production of conditioned freezing (Iwata *et al.* 1986; Le Doux *et al*. 1988). In this context it is interesting that the autonomic (as opposed to the freezing) component of conditioned fear appears to be mediated by the lateral rather than the medial hypothalamus. 'The conditioned coupling of changes in arterial pressure and emotional behaviour to auditory stimuli involves the relay of the acoustic signals through the

inferior colliculus to the medial geniculate body and from there to the amygdala. Since both direct and multisynaptic connections exist between the amygdala and the lateral hypothalamus, [this suggests] . . . a pathway linking the primary acoustic system with autonomic neurons in the spinal cord' (Iwata *et al*. 1986, p. 165).

We should also bear in mind the possibility that the diffuse activation of the DMH by chemical stimulation (see Shekhar 1994) may produce an abnormal pattern of activation which (like, perhaps, activation of multiple, high-intensity, mutually incompatible directed escape programmes) would simply function to activate the PAG and so remove the conflict by engendering undirected escape. If this is true there may be less similarity between the DMH and the PAG in terms of the normal control of behaviour than is suggested by the chemical stimulation results.

While we have had good reason to see descending output from the PAG and the MH as providing output from successive hierarchical levels of the FFFS, there also appears to be some involvement of ascending output from the medial hypothalamus in the BIS and hence anxiety (as opposed to panic). Activation of the DMH results in direct or indirect activation of the medial supramammillary nucleus (Silveira *et al*. 1995; from which it also receives input, Vertes 1992) and both the DMH and the medial supramammillary nucleus are components of an ascending system controlling the frequency of hippocampal theta activity and are sites at which benzodiazepines act directly to alter theta (see Appendix 5; but note that the part of the DMH involved in the control of theta may not be the same as the cardiostimulatory area; Shekhar, personal communication). We argue in this book that theta is fundamental to correct operation of the BIS. Anxiolytics also act on the DMH to reduce the aversive reaction produced by DMH stimulation (Milani and Graeff 1987) and muscimol in the DMH suppresses the cardiac reaction to air stress (Stotz-Potter *et al.* 1996). We have already noted that GABA blockade of the MH has 'anxiolytic' effects in the plus maze. However, it has been shown that these latter behavioural effects are not a consequence of the accompanying changes in autonomic reactions (Shekhar *et al.* 1993) and DMH lesions do not produce an 'anxiolytic' effect in the social interaction test (Inglefield *et al*. 1994).

The elicitation of rearing from the DMH (Silveira and Graeff 1992) also suggests a link with anxiety (see Chapters 2 and 5) and monoamine levels in this area predict the level of separation-induced vocalization in guinea-pig pups in a novel environment (Harvey *et al*. 1994) and are elevated by the conditioning used in the fear-potentiated startle test (but not by footshock or acoustic startle alone, Shekhar *et al*. 1994; however, lesions of the DMH increase startle, Inglefield *et al.* 1994).

We are left, then, with a picture of a profusion of nuclei, or subregions, in the medial and lateral hypothalamus and periaqueductal grey, each controlling its own specific component of functional output. Different environmental conditions produce different patterns of apparently coordinated output of the behavioural and autonomic systems by activating different sets of these nuclei—or more probably by activating all of these nuclei but in different patterns of intensity. At least part of the resultant coordination of responses comes from the inhibition, by 'higher' or 'parallel' but more intensely active levels of the system, of responses or components of responses which would otherwise be produced and would interfere with the response being produced. Thus, not only is there, as suggested by Le Doux, 'quick and dirty' analysis of threatening stimuli at the bottom of a hierarchically organized sensory system (where the higher levels can override the lower levels), but there is also 'quick and dirty' production of basic defensive responses (including uncoordinated escape and aggression as

well as autonomic activity) which can be overridden by more sophisticated and directed escape responses.

It is quite clear from the organization of inputs to the PAG that quick and dirty or slow and sophisticated stimulus analysis can each result in either quick and dirty or slow and sophisticated responding. There is no necessary functional or anatomical requirement for the level of stimulus processing to match the level of response programming. Thus a partially digested stimulus arriving at high speed via the quick and dirty stimulus processing system, if it were of sufficient intensity, could release both the MH and the PAG. Given that a suitable escape route were sufficiently obvious, the MH would inhibit the PAG and the result would be coordinated escape. Conversely, it might require extensive stimulus processing (and indeed the most tortuous deduction) by the highest cortical levels for someone to realize that they are in fact in a lethal trap from which there is no obvious route of escape. In the absence of inhibitory input from the MH the resultant activation of the defence system would flow out through the PAG in the form of a panic attack.

The diffuse involvement of a range of nuclei in even simple responses is also suggested by the fact that unilateral chemical (or electrical) activation of the MH which elicits ‘flight behaviour of moderate intensity . . . [also increases activity] ipsilaterally in the piriform and entorhinal cortices, in several amygdaloid nuclei, in the bed nucleus of the stria terminalis, in the septo-hypothalamic nucleus, in the paraventricular, anterior and dorsomedial hypothalamic nuclei, in the paraventricular thalamic nucleus, in the dorsal periaqueductal grey extending to the cuneiform nucleus, and bilaterally in the supramammillary decussation and the locus coeruleus’ (Silveira *et al*. 1995, p. 265). This same pattern of activation appears to occur with DMH or PAG stimulation and with natural activation by pain and stress (see Sandner *et al*. 1993). These ‘results suggest that there is a neural substrate that mediates aversive behaviour, no matter how it is produced’ (Sandner *et al*. 1993, p. 9). However, it is also clear that small shifts in this pattern occur depending on whether the PAG or the MH is the primary source of the activation—with notable consequences for some responses such as aggression.

The possible roles for activation by the MH of the limbic cortex,[4] supramammillary area, and locus coeruleus will all be considered in later appendices. However, in the context of the hierarchical defence system which we are now tracing retrogradely, the amygdala and the structures related to it appear most closely related in function and are our next area of interest.

A2.4 The amygdala—when is a defence system not a defence system?

Here, we will look at the amygdala in the context of the descending defence system which we have been tracing backwards into the brain. However, as we will see, the *efferent* connections of the amygdala also ascend to link it intimately with a wide variety of limbic and posterior cortical areas, and do not merely descend to link it with the MH, PAG and related areas. Whether or not these ascending connections are present to cope with defensive situations, it is clear that they allow the amygdala to influence stimulus processing, and hence potentially memory, quite extensively.

It is also clear that lesions of the amygdala produce much wider emotional deficits (the Klüver–Bucy syndrome) than would be expected if it were a purely defensive structure (see, for example, Le Doux 1992). Thus while the amygdala can certainly be viewed as the primary central structure controlling responses to actual (as opposed to potential) threat (Le Doux 1994), it can also be viewed as the means whereby, quite generally, 'sensory stimuli are endowed with emotional and motivational significance . . . Thus, when the amygdala is damaged, monkeys act tame in the presence of humans because the sight of a human is no longer coded as a threatening stimulus. Similarly, '*dietary and sexual preferences change since environmental stimuli no longer elicit their normal affective responses*' (Le Doux 1992, p. 340, our emphasis). Likewise, the 'amygdala . . . influences maternal behaviour by relaying olfactory input to the medial preoptic area' (Numan 1994, p. 19) and appears to have a related transducer role in mating (Malsbury and McKay 1994; Minerbo *et al*. 1994; Kondo and Arai 1995) and paternal behaviour (e.g. Kirkpatrick *et al.* 1994*a*) as well, probably, as in salt control (e.g. Seeley *et al*. 1993), food intake (e.g. King *et al*. 1993; Crovetti *et al*. 1995), and social interaction (e.g. Adolphs *et al*. 1994; Borlongan and Watanabe 1994; Kirkpatrick *et al*. 1994*b*). In human beings it has been suggested that 'the amygdala plays important roles in memory and in the modulation of social and emotional behaviour' (Tranel and Hyman 1990, p. 349).

Some care must be taken, however, if we are not to ascribe too broad a set of functions to the amygdala. It is located within the temporal lobe and closely connected to areas such as the hippocampus and entorhinal cortex. As a result, lesions to it, or stimulation of it, will not only influence these other areas because of its connections with them, but can also influence fibres of passage within and at the border of the amygdala. These fibres of passage can often be crucial for temporal lobe functions which are completely independent of the amygdala. The recent tendency to use injections into the amygdala is, therefore, to be welcomed.

To note just one example: taste aversion conditioning is impaired by conventional, but not cytotoxic, lesions of the amygdala (see Le Doux 1992, p. 341), unless the cytotoxic lesions are made in the basolateral nucleus (Yamamoto *et al*. 1994).

In dealing with the amygdala, then, we will follow a strategy which we will subsequently apply on a much larger scale to the septo-hippocampal system. We will attempt to combine the anatomical, lesion, and physiological data into a coherent picture, in the hope that each discipline will correct the faults inherent in the others. We will also concentrate on the role of the amygdala in anxiety and omit, for example, any discussion of its possible role in the symptomatology of depression (e.g. Schulkin 1994; Schulkin *et al.* 1994). We start with anatomy because its results (as opposed to their interpretation) are least likely to be overturned by findings in the other disciplines.

A recent review of the anatomy of the primate 'amygdaloid complex' is provided by Amaral *et al*. (1992). We will follow their review closely and where no reference is given for any specific anatomical fact, their review is the source. Pitkänen *et al.* (1997; see also Savander *et al.* 1997*a*) provide a recent detailed update of the internal circuitry of the rat amygdala which diverges from that of Amaral somewhat in emphasizing reciprocal connections between the lateral and basal complexes (but still retains the idea of a largely unidirectional link between these and the corticomedial complex), but concludes that 'the connectional organization of the monkey amygdala is similar to rather than different from that of the rat' (Pitkänen *et al.* 1997, p. 522).

A2.5 The amygdala: intrinsic anatomy

The use by Amaral *et al*. (1992) of the term 'amygdaloid complex' emphasizes that the amygdala can be subdivided into a number of distinct nuclei.

The precise divisions of the amygdala are likely to vary between species, as indeed are the connections of the amygdala as a whole. However, lesion studies frequently involve the entire structure and, even in the primate, partial lesions will involve groups of nuclei. Similarly, the extensive connections made between nuclei in the amygdala give us some excuse for treating it as a functional whole. So, although much more detailed analysis would be preferable, we will provide here only a general overview.

A convenient starting point for an analysis of the connections of the amygdala with other structures is the known connections within the amygdala. 'In the monkey, as in nonprimate species, there is general agreement that the major intra-amygdaloid connections arise in the lateral and basal nuclei and terminate in the more medial nuclei. The accessory basal nucleus also projects to the central, medial and cortical nuclei and to the amygdalohippocampal area. Since there are only weak projections from the medial, cortical or central nuclei, or the amygdalohippocampal area back to the lateral and basal nuclei, the intrinsic flow of information through the amygdala is primarily unidirectional and follows a lateral to medial direction' (Amaral *et al*. 1992, p. 26, see Fig. 4.4; and see Savander *et al*. 1996 for similar findings in the rat; but see Savander *et al*. 1997*b* for contrary evidence on unidirectionality in the rat). This largely unidirectional flow is unusual within the limbic system and is shared only by the hippocampal formation.

The lateral nucleus projects directly or via one synapse to virtually all the other nuclei of the amygdala (see Pitkänen *et al*. 1995), making what appear to be predominantly excitatory, glutamatergic connections (Smith and Paré 1994). The same is largely true of the basal nucleus. (This effectively consists of basolateral and basomedial nuclei and so will be called the basal complex, below.) The lateral nucleus receives very few inputs from amygdaloid nuclei other than the basal nucleus (and even these are sparse). Likewise, the basal nucleus receives few inputs (although more than the lateral) from nuclei other than the lateral nucleus. The lateral and basal nuclei both have complex intranuclear connections. There might seem some basis, then, for treating the lateral and basal nuclei as a fairly coherent laterobasal complex which can be viewed primarily as an input processing unit for the remainder of the amygdaloid complex. However, the differentiation of their non-amygdaloid connections, coupled with the weakness of the return projection from the basal to the lateral nucleus, makes it better to treat them as quite separate stages of input to the rest of the amygdala. On this view, the return projection from the basal to the lateral nuclei is just a weak example of the tendency to feedback connection between levels which we will see is characteristic of the septo-hippocampal system and its cortical afferents (Appendix 4) and, to an even greater extent, of the neocortex, particularly the frontal cortex (Appendix 3).

The remaining nuclei of the amygdaloid complex all receive input from the lateral nucleus either directly or (in the case of the amygdalohippocampal area) via one synapse. Also, as far as can be told at present, they all appear to be richly reciprocally connected with each other, with most of the nuclei projecting to and receiving projections from most of the other nuclei, thus forming, in essence, a multinodal net (where each node is a nucleus). Recently, it has become apparent that the intercalated cell masses which divide the basolateral nuclei from the centromedial nuclei consist almost entirely of GABAergic cells (Pitkänen and Amaral 1994)

which have as their virtually sole telencephalic efferent target cells in the substantia innominata and the horizontal limb of the diagonal band (Paré and Smith 1994). These are likely to be of major functional significance in the control by the amygdala of the basal forebrain cholinergic system and hence of the telencephalon generally (and it may be significant, in this context, that the intercalated cell masses receive heavy dopaminergic innervation; Fallon and Ciofi 1992). So little is known about their connections and functional significance; however, that they will be ignored below.

For the purposes of the remaining review of the connections, and functions, of the amygdala, we (as in Fig. 4.4) will treat it as consisting of three major divisions: the lateral nucleus, basal complex, and corticomedial complex.[5] Our analysis will proceed from lateral to medial following the main flow of information through the amygdaloid complex. Although our discussion of the corticomedial complex will be based on results from analysis only of nuclei conventionally assigned to the amygdaloid complex, it should be noted that there is good reason to include in a single 'diagonal ventral forebrain continuum . . . the central nucleus of the amygdala, the sublenticular portion of the substantia innominata, and the lateral bed nucleus of the stria terminalis' (Schmued 1994).

A2.6 The amygdala: connections of the lateral nucleus

The lateral nucleus, as we have seen, is a major gateway to the rest of the amygdala. As such, its afferent connections are of particular interest and we will deal with these first. The lateral nucleus receives gustatory, visceral, auditory, and visual input from the thalamus and also receives extensive unimodal and polymodal input from sensory neocortex which 'provide it with rather high-level information concerning potentially all aspects of ongoing sensory experiences' (Amaral *et al*. 1992, p. 55).

In the visual case, it is of particular interest that the amygdala receives cortical input only from the highest level of processing (inferotemporal cortex) and does not receive input from earlier cortical levels (striate and prestriate; see McDonald and Mascagni 1996 for similar findings in the rat), although, as Le Doux (1994) has emphasized, it does receive input from *precortical* stages of visual processing. The same type of parallel organization is present for the auditory input also. Thus there is an input from the non-laminated division of the medial geniculate (Shinonaga *et al.* 1994) and a topographically organized input from temporal cortex area TE and perirhinal cortex, but not primary auditory cortex (Romanski and Le Doux 1993; Stefanacci *et al.* 1996). So, parallel precortical and final (but not intermediate) cortical sensory inputs to the amygdala may be quite general.

The lateral nucleus has connections both to and from the insular cortex of the frontal lobe. However, these connections should probably not be viewed as reciprocal. The part of the lateral nucleus which receives projections from the insula is different from the part which sends projections to it. The insular input to the amygdala 'provide[s] the most direct route for somatosensory information to reach the amygdala' (Amaral *et al*. 1992). The return projection from the amygdala could, then, fulfil a similar function to the return projections from the amygdala to the various levels of the visual system.

The lateral nucleus receives an extensive serotonergic innervation which we will discuss briefly towards the end of this appendix, and in much greater detail in Appendix 10.

The lateral nucleus appears to have no major subcortical efferent projections, with the exception of the mediodorsal thalamic nucleus with which we will deal later, together with the frontal cortex.

In contrast to this, the lateral nucleus is one of the main sources of substantial efferents from the amygdala to the septo-hippocampal system. 'The hippocampal projection back to the amygdala, by comparison, seems rather meager. . . . Thus, there appears to be a polarity to the amygdalo-hippocampal interconnection' (Amaral *et al*. 1992, p. 40; but see Le Doux 1994). Stimulation of the hippocampal formation produces a monosynaptic excitatory response in less than 10 per cent of cells, but about half can be activated polysynaptically (Mello *et al.* 1992). This polarity makes it much more likely that the lateral amygdala sends the hippocampus information about threat (see Desmedt *et al.* 1998) than that the hippocampus sends the amygdala very high-level information about stimuli—but these alternatives are not mutually incompatible.

We will discuss amygdalo-septo-hippocampal and cortico-septo-hippocampal connections in much greater depth in Appendix 4. However, it should be noted here that the hippocampal formation receives as extensive cortical input as does the amygdala. This strongly suggests that the hippocampus will receive information about the sensory qualities of stimuli directly from the cortex and can receive additional information about the affective qualities of those same stimuli from the amygdala. However, the extensive recursion of hippocampal connections with most areas (Appendix 4), many of which have connections to the amygdala, makes it difficult to take this argument too far. The combination of partial polarity with an overall recursion is particularly well exemplified by the connections of the amygdala to the visual cortex, which we will discuss in the section on the basal nucleus.[6]

The lateral nucleus does not appear to project directly to any part of the frontal or cingulate cortex (other than the insular projection mentioned). The lateral nucleus can influence the frontal cortex via a synaptic relay, the mediodorsal thalamic nucleus. We will discuss this projection shortly, together with the other amygdaloid projections to the mediodorsal thalamus.

It is not clear what information the input from the caudal orbital cortex might carry, but on our analysis so far, it appears that we can characterize *all* inputs to the lateral nucleus as carrying sensory information (albeit in some cases very highly processed) which could be used to detect the presence of threat (or other affect-relevant situations). As we will see below, this sensory input will often constitute the conditioned stimulus (CS) for conditioned aversive reactions, the conditioning of which occurs within the remainder of the amygdala. Likewise, we can provisionally characterize *all* the output of the lateral nucleus as providing some kind of signal of threat (or detection of some other affect-relevant situation) to either the hippocampal formation (particularly the rostral entorhinal cortex), the mediodorsal thalamus, or the rest of the amygdala.

A2.7 The amygdala: connections of the basal nucleus

As we have noted already, the basal nucleus receives a major input from the lateral nucleus and, hence, is privy to essentially the same information as the lateral nucleus, but in a more processed form. There is little if any input from the unimodal sensory cortex, and only

modest input from the polysensory cortex (which may itself be a more direct copy of input also sent to the lateral nucleus; see, for example, Romanski and Le Doux 1993) and it receives some excitatory input from the prefrontal cortex (Brinley-Reed *et al*. 1995). To a fair extent, then, the basal nucleus can be viewed as providing a second stage of processing of information largely received from the lateral nucleus.

In this context, it is interesting that the basal nucleus has extensive projections to all stages of visual processing in the cortex. Thus, it receives visual information (relayed to it by the lateral nucleus) only from the highest level of the visual hierarchy. It returns information directly not only to this highest level but also to intervening levels and to the primary visual (striate) cortex. The simplest explanation of this organization is that the basal nucleus sends an, at least partially digested, affective signal to bias each stage of the visual system to more efficient (attentionally loaded or perhaps negatively biased) processing of information while it itself receives from the visual system (via the lateral nucleus) only the most highly processed and accurate of affect-relevant visual input.

There is input from the midline thalamus (excluding the mediodorsal nucleus, which does not project to the amygdala), and this appears to form one part of a loop from the thalamus to the basal nucleus to the corticomedial amygdaloid complex and back to the thalamus. 'The cortical projections [to the amygdala], which arise from secondary and polymodal association cortices, probably relay cognitive, but otherwise affectively neutral, information pertaining to sensory stimuli. Information concerning the aversive properties of stimuli are probably relayed separately via projections from the external lateral part of the parabrachial complex, the dysgranular insular cortex, and midline and intralaminar thalamic nuclei, each of which receives nociceptive inputs and projects to the basolateral complex' (Davis *et al.* 1994, p. 209).

The basal nucleus has reciprocal connections with the hippocampus proper and also receives input from the entorhinal cortex. These connections will be discussed in greater detail in Appendix 4. However, it should be noted here that the interconnection between the basal nucleus and the hippocampus proper is the only connection between these two structures that does appear reciprocal (with the others being predominantly from the amygdala to the hippocampus). This reciprocal projection is particularly surprising in that it terminates in and arises from the boundary between area CA1 and the subiculum, where the CA1 pyramidal layer overlies that of the subiculum. Other projections to and from the hippocampus are general to one, or several, fields. However, in this case, the remainders of these two cell fields are not involved. This suggests that this connection has some special function unrelated to the normal flow of information through the hippocampus. What this function may be is unknown, but we will consider the matter further in the context of the septo-hippocampal system. In particular, we will argue that the organization of this output from the hippocampus and the fact (Maren and Fanselow 1995) that it can show long-term potentiation (LTP, see below) are consistent with the treatment, by the hippocampus, of the amygdala as just one of a wide variety of motor control areas which are topographically mapped into the hippocampus (Appendix 4). There is also evidence that prior acquisition of information can, via the hippocampus, interfere with amygdaloid information storage (McDonald and White 1995).

It should be noted that electrophysiological estimates of the proportion of basal nucleus cells monosynaptically activated from the hippocampus (e.g. 20 per cent, Mello *et al*. 1992) could be greatly underestimated if care is not taken to stimulate the CA1–subiculum boundary.

Certainly, as many as 60 per cent of these cells (both projection cells and interneurons) show modulation related to the hippocampal theta (Paré and Gaudreau 1996; see also Paré *et al.* 1995*b*). On the other hand, the monosynaptic input from the basolateral nucleus to the hippocampus can show LTP and lesions of the basolateral amygdala can attenuate dentate LTP, so it is clear that the amygdala can also control the hippocampus (Ikegaya *et al.* 1994; Desmedt *et al.* 1998).

An important point to note in relation to the memorial functions of the amygdala, which we will consider shortly, is that the basal nucleus (like the corticomedial complex) projects to the cholinergic basal forebrain, particularly the basal nucleus of Meynert and the horizontal limb of the diagonal band complex. It also receives an extensive return projection from this area which is one of the densest cholinergic inputs to any forebrain area. These two projections are not reciprocal as the input is to the magnocellular division of the basal nucleus of the amygdala, while the output is from its parvicellular division. This source of cholinergic innervation (or at least its biochemistry) appears to be distinct from that of the cholinergic innervation of the corticomedial complex (Heckers and Mesulam 1994).

We will consider the possible function of this cholinergic input in Appendix 10, together with our consideration of the dense serotonergic and moderate dopaminergic and modest noradrenergic input to the parvicellular division.

The basal nucleus also projects to the bed nucleus of the stria terminalis, but we will consider this in the next section. The ventromedial hypothalamic nucleus sends a weak projection to the lateral nucleus, but this can be viewed as, in effect, a weak return loop for the much stronger projection from the corticomedial complex to the ventromedial hypothalamus (this is dealt with in the next section).

Unlike the lateral nucleus, the basal nucleus has substantial (largely unidirectional) subcortical projections. This is likely to be a first stage of relatively unprocessed output from the amygdala to motor control areas. The basal nucleus (and accessory basal nucleus) projects to the striatum as a whole: the caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, and (weakly) to the ventral pallidum (which, however, receives a strong projection from the nucleus accumbens). In the same way that we argued that the projection from the lateral nucleus to the hippocampus was likely to carry a very crude threat signal (or signal of other affective significance), it seems likely that this projection from the basal nucleus carries a (slightly more sophisticated, but still relatively global) threat signal to the dorsal and ventral striatum, which are known to be important for motor control and particularly for the learning of new responses. These connections could, therefore, provide one route for the elicitation and fine-tuning of learned avoidance responses (particularly where the required response is not part of the species-specific defence repertoire). In the case of the ventral striatum (nucleus accumbens), at least, the amygdalar projections are topographically organized and connect with medium-sized spiny neurons which are also in receipt of dopaminergic input and, perhaps, input from the subiculum (Johnson *et al.* 1994*a*,*b*; Wright *et al.* 1996). Basolateral amygdala cells appear to synapse on cells in the ventral striatum which, in turn, project to the lateral hypothalamus and it has been suggested that this is the basis for the control, by the amygdala, of autonomic responses (Kirouac and Ganguly 1995; see also Callaway *et al.* 1991).

The basal nucleus (like the lateral) projects to the mediodorsal thalamus, which provides a relay to prefrontal cortex. Unlike the lateral nucleus, the basal nucleus also has direct,

topographically organized, projections to the agranular insular cortex, lateral orbital cortex, medial orbital cortex, and the medial wall of the frontal lobe. The connection to the medial prefrontal cortex appears to involve a modest excitation of principal cells coupled with extensive feedforward inhibition (Bacon *et al*. 1996). There is also a modest projection to the anterior cingulate cortex. There is almost no projection to the dorsolateral prefrontal and premotor cortices.

Given the essentially unidirectional projection to the striatum, one might think that the direct and indirect projections to the frontal and cingulate cortices would merely send partially processed affective signals to the highest levels of the motor system. However, many of these non-striatal projections may be reciprocal. Thus the connections between area 46 (on the lateral surface of the prefrontal cortex) and the basal nucleus arrive in and depart from the magnocellular division; the connections between the insula and the basal nucleus arrive in and depart from the parvicellular division. Given the possible role of the frontal cortex in working memory (see Appendix 3), it seems possible that the amygdala sends to the frontal cortex affective information akin to that which it sends to the striatum and receives from the frontal cortex working memory information (representing predictions) akin to the current sensory information which it receives from the lateral nucleus.

A2.8 The amygdala: connections of the corticomedial complex

As we discussed earlier, the extensive reciprocal interconnections of the more medially and superficially placed amygdaloid nuclei have led us, for the purposes of this review, to treat them as a functional unit: the corticomedial complex.

From within the amygdala the complex receives input from both the lateral and basal divisions. All of the nuclei except the amygdalohippocampal area and posterior cortical nucleus receive input from the lateral nucleus, while all of the nuclei except the anterior cortical nucleus, the anterior amygdaloid area, and the posterior cortical nucleus receive input from the basal nucleus. The net effect is that all of the nuclei of the complex receive direct, or nearly direct, input from both the lateral and the basal nuclei. They can be viewed, therefore, as being provided with the same information as that which the early stages of the amygdala send to the hippocampus, frontal cortex, cingulate cortex, and striatum. They will also receive whatever modifications to this information are provided by the return loops from the frontal and cingulate cortices.

The complex receives inputs from the midline and posterior thalamus, but these are matched by projections from the complex to the same areas of the thalamus. Since the origin of the projections to the thalamus is the same as the target of the projections from the thalamus (the central and medial nuclei), and since there is no other direct source of sensory input to the corticomedial complex, it seems most parsimonious to assume that the complex sends to the thalamus processed affective information and receives, in return, a feedback signal, related to the thalamic response to this affective input which allows fine-tuning of its effect on the thalamus.

This interaction between the corticomedial complex and the thalamus could well be on a par with the reciprocal connections of the basal nucleus with visual cortical areas.

The complex receives noradrenergic and serotonergic input but, unlike the basal nucleus, receives little cholinergic input and instead receives considerable dopaminergic input from the substantia nigra and ventral tegmental area, A10 (Fallon and Ciofi 1992). The very minor cholinergic input appears to have a somewhat different origin, or at least different biochemistry from that of the input to the basolateral area (Heckers and Mesulam 1994). All of these systems will be discussed in Appendix 10.

As we noted above, the basal nucleus of the amygdala projects to the bed nucleus of the stria terminalis. This would allow it to influence indirectly a variety of hypothalamic and brain stem areas which also receive direct projections from the corticomedial complex (and which we will consider shortly). Given this organization, and the extensive interconnections of the corticomedial complex, it seems reasonable for our present purposes to treat the bed nucleus as being, in functional terms, just another part of the corticomedial complex. After all, we have already amalgamated a large number of different nuclei into this complex. As we noted earlier, the sublenticular portion of the substantia innominata can also be included in this complex and the whole has been termed the 'diagonal ventral forebrain continuum' (Schmued 1994). Strictly it is the lateral bed nucleus which Schmued includes in this continuum and it is to be noted that stimulation of the medial bed nucleus produces opposite effects on the cardiovascular system to stimulation of the lateral nucleus (Dunn and Williams 1995). However, our amalgamation of a large number of nuclei into the 'corticomedial complex' will have included many nuclei, and neurons within nuclei, with differing output targets and effects. It is the sharing of a more general function and overall patterns of innervation that justifies the amalgamation, at least for the purposes of simplification in a general review such as this.

As we described in more detail for the basal nucleus, the corticomedial complex projects to the basal forebrain areas thought to be involved in the cholinergic control of memory. This projection to the cholinergic basal forebrain allows the central nucleus of the amygdala to increase neocortical arousal (Kapp *et al.* 1994). 'The fibres which innervate the cholinergic nuclei sweep through the basal forebrain, and apparently continue on to the thalamus, hypothalamus and brain stem' (Amaral *et al*. 1992, p. 31). Thus, the same, presumably highly processed, signal is sent to all these areas.

We have already considered the thalamic projection. The hypothalamic projection makes connection with the anterior hypothalamus, the supraoptic and paraventricular nuclei, and substantially in the ventromedial hypothalamus (which sends a modest return projection) and the premammillary nuclei. It also makes connections with the lateral hypothalamus as a whole, the paramammillary, tuberomammillary, and supramammillary nuclei. The projection then continues towards and into the spinal cord while making connections with 'a number of structures that have been implicated in autonomic control including the periaqueductal grey, the parabrachial nucleus, the dorsal vagal nuclei, and the reticular formation. Many of these structures also send ascending fibres to the amygdala' (Amaral *et al*. 1992, p. 35). This general organization appears just as true of the diagonal ventral forebrain continuum as a whole as it does of the central nucleus of the amygdala in particular (Schmued 1994).

From this we can see that the main input to the corticomedial complex is processed, presumably affective, information from the lateral and basal nuclei, potentially filtered by interaction between the basal nucleus and the frontal and cingulate cortices. The main output from the corticomedial complex is to the thalamus, hypothalamus, brain stem, and spinal cord, although there is also evidence for an output to the hippocampus which can both show

LTP (see below) and act cooperatively with perforant path input to the dentate gyrus (Ikegaya *et al*. 1995*a*). Its targets are largely areas which we have so far considered as parts of the hierarchical defence system, including some of the structures presumed to be controlled by the periaqueductal grey, or else they are the sensory systems which can provide the amygdala with information about threat.

While we have lumped parts of the corticomedial complex together and focused on defence, it should noted that its functions are broader than this and that different parts of it are likely to be specialized for each of these functions. Thus, for example, reproductive and agonistic behaviour appear to be mapped into distinct areas (Canteras *et al.* 1995).

A2.9 The amygdala: overview of the anatomy

We now have a view of the amygdala as receiving, in the lateral nucleus, information which can be used to identify threat (and related affective situations). In its crudest form this information is sent from the lateral nucleus to the hippocampal formation (particularly the entorhinal cortex) and to the dorsomedial thalamus, as well as to the basal nucleus of the amygdala. In each case there is little feedback.

The basal nucleus has an unusually reciprocal (and unusually restricted) connection with the hippocampal formation and also has extensive reciprocal connections with the frontal and cingulate cortices. In the latter case, we suggested that the projection to the cortex provided information about affect, the return projection provided information about current plans (essentially read out from working memory), and the reciprocity would allow a recursive updating of current plans in the context of the predicted affective consequences. When we discuss the septo-hippocampal system in detail, we will argue for a roughly similar, but more hippocampopetal, organization. The basal nucleus also provides output to all levels of visual processing in the cortex which we argued could provide an affective bias to the processing of incoming information. The main clearly unidirectional output of the basal nucleus was to the striatum where, we argued, it could provide affective bias to ongoing motor plans and their modification.

The corticomedial complex receives information from both the lateral and basal nuclei. In the latter case this opens the possibility that the corticomedial complex takes into account not only the primary affective information being determined in the lateral nucleus but also the interaction between that information and concurrent processing in the frontal cortex, cingulate cortex, and hippocampal formation relayed via the basal nucleus. Its primary output, in contrast to the basal nucleus, is subcortical and appears to involve (if we take defence systems as our cue) interaction with the ‘lower’ levels of affective control for which the amygdala represents one of the higher levels.

It has recently become evident that ‘each portion of the prefrontal cortex has a distinctive projection to the amygdala. The ventral areas of the lateral and medial prefrontal cortices, which receive olfactory projections, are the only prefrontal cortical areas with projections to the olfactory-related superficial amygdaloid nuclei. The more dorsally situated prefrontal areas, the dorsal agranular insular area and prelimbic cortex have complementary projections to the basal nucleus’ (McDonald *et al.* 1996). The amygdala, then, may share the principles of organization which we will discover for the frontal cortex in the next appendix.

A2.10 The amygdala: effects of lesions

We now have an anatomical skeleton of the amygdala which we need to flesh out with function. To some extent, in discussing the anatomy we previewed aspects of function, but here we want to look at the possible functions in more detail. As we noted previously, a word of warning is required. Lesions to the amygdala will often encroach on other areas and, in particular, fibre pathways. Specific cytotoxic lesions, or discrete electrolytic lesions, can, then, produce more restricted effects than do conventional large electrolytic lesions.

The effects of amygdala lesions have been extensively reviewed by Sarter and Markowitsch (1985) and more recently by Davis (1992*a*) and Aggleton (1993). Our conclusions in this and the following sections are based largely on Davis (1992*a*), but where a reference is not given for any particular fact it will be found in one of these three reviews.

The key point for our search for the neurology of anxiety is that 'converging evidence now indicates that the amygdala plays a crucial role in the development and expression of conditioned fear' (Davis 1992*a*, p. 353). We will discuss shortly the possible basis for conditioning of fear in the amygdala. However, a point which Davis mentions but does not emphasize (in contrast to Le Doux 1993; and Helmstetter 1992) is that the amygdala is clearly involved in unconditioned fear as well as conditioned fear and is one of the higher levels of the system of nuclei which becomes generally active in a wide variety of aversive situations (e.g. Sandner *et al*. 1993).

Lesions of the amygdala impair unconditioned flight, aggression, and defensive reactions in general. They increase a rat's contacts with a cat, decrease freezing induced by a dominant rat, and produce a general 'taming' effect. They decrease the capacity of a novel stimulus to elicit release of adrenocorticotrophic hormone (ACTH) and corticosterone, and they decrease stress-induced ulceration. They reduce the analgesia produced by exposure to a cat, acute footshock, and a situation in which the animal was previously exposed to footshock (Fox and Sorenson 1994). All of this suggests that the role of the amygdala is not specific to conditioned reactions. By contrast, lesions of the amygdala do not prevent the animal from eating and drinking or from learning a variety of positively reinforced discriminations (T-maze, pattern discrimination, object discrimination, delayed response, delayed matching-to-sample, order discrimination, and some discrimination reversals—for the last three, see Mumby *et al*. 1995). Nor does it appear to be involved in latent inhibition (Weiner *et al.* 1995), something which we will return to in Appendix 9. The amygdala, therefore, appears to be involved more extensively in reactions to aversive stimuli than appetitive stimuli—but this bias is not exclusive (an issue we will discuss further below). For example, lesions of the medial (but not the basolateral) amygdala produce a major deficit in copulatory behaviour (Kondo 1992) and GABA agonist injections decrease food intake (Minano *et al*. 1992). Nonetheless, as Le Doux (1996, p. 191) emphasizes: 'a pure amygdala lesion had no effect on delayed nonmatching to sample. Importantly, though, the pure amygdala lesion did produce the emotional concomitants of the Klüver–Bucy syndrome, especially reduced fear.' This clearly distinguishes, then, the amygdala from the hippocampus. (Precise procedural details are important for the sensitivity of memory tasks to lesions, see Chapter 6, but when amygdala and hippocampal lesions are directly compared across a battery of tasks their effects can be dissociated; Raffaele and Olton 1988; Kesner and Williams 1995; Mumby *et al*. 1995).

As would be expected from the results with unconditioned responses, lesions of the amygdala have a wide range of effects which are consistent with an impairment of fear mechanisms in conditioned response paradigms. They impair one-way and two-way active avoidance, passive avoidance, operant conflict, conditioned emotional response, freezing (to a CS for shock and in passive avoidance tasks and in explicit apparatus-shock conditioning), conditioned hypoalgesia, autonomic reactions to a CS for shock (see La Bar *et al*. 1998 for analogous effects in human subjects), and fear-potentiated startle (but not unconditioned startle). In relation to our analysis of the hippocampus, it is noteworthy that the effects of amygdala lesions on conditioned freezing appear more extensive than those of hippocampal lesions (J. J. Kim *et al.* 1993—but note that their hippocampal lesions were proportionately smaller than their amygdalar lesions) while they have no apparent effects on water maze learning (Decker *et al.* 1995).

In keeping with our equation (Chapter 3) of Pun+/CS-Pun+ with Rew–/CS-Rew–, amygdala lesions also impair the double-runway frustration effect (but not extinction or the partial reinforcement extinction effect; Henke 1977), differential reinforcement of low rates of response, spatial delayed alternation, discrimination reversal, win stay/lose shift, and negative contrast (this last with cytotoxic as well as conventional lesions; Salinas *et al.* 1996). Like anxiolytic drugs, amygdala lesions also impair positive contrast. However, as we discussed in Chapter 3, this result is difficult to link to the results in other tasks at the theoretical level. Lesions of the central (but not basolateral) amygdala impair memory for location of a large food reward in an eight-arm maze where all the other arms contain a small reward, suggesting that the amygdala may be involved in memory for reinforcement 'providing the reinforcement input is of sufficient intensity and duration to elicit a relatively strong emotional or affective reaction' (Kesner *et al.* 1989).

There are a number of results which do not fit simply into the picture we have been building of the amygdala as a general controller of fear and related aversive emotional states. 'Fiber-sparing chemical lesions of most of the amygdaloid complex . . . attenuate avoidance of thirsty rats to approach an electrified water spout. . . . Importantly, however, these same lesioned animals did not differ from controls in the rate at which they found the water spout over successive test days or their avoidance of the water spout when quinine was added to the water. . . . [Likewise], ibotenic acid lesions of the amygdala fail to block taste aversion learning' (Davis 1992*a*, pp. 362–3). Similarly, while they do affect shock-probe avoidance, they do not affect defensive burying (Treit and Menard 1997; Treit *et al.* 1998). While it is possible (as Davis suggests) that these results show a specificity of the amygdala to tasks involving an obvious fear component, this is difficult to reconcile with the involvement of the amygdala in tasks involving omission of reward and with such behaviour as cocaine-induced conditioned place preference (Brown and Fibiger 1993).

It should be noted, in passing, that while lesions of the central nucleus of the amygdala do not affect taste aversion learning, lesions of the basolateral nucleus do produce an impairment. This latter 'is more severe than that induced by gustatory cortex lesions, but is less severe than that caused by parabrachial nucleus lesions. Combined lesions of amygdala and gustatory cortex completely disrupted conditioned taste aversion acquisition, indicating that these two structures are essential for conditioned taste aversion formation and that, if one of them is eliminated, weak conditioned taste aversions can be established with the other structure. On the other hand, retention of conditioned taste aversions is almost completely disrupted by lesions of the basolateral amygdala' (Yamamoto *et al*. 1994, pp. 129–30, and 1995; see Gallo *et al*. 1992 for similar results with temporary inactivation; see Ferry *et al.*

1995 and Hatfield and Gallagher 1995 for related data on taste-potentiated odour aversion). This suggests that different parts of the amygdala are involved in different types of aversive conditioning and that, even in cases where the amygdala appears to be the repository of a specific 'memory trace', it is not the only structure which can support that particular type of learning.

The picture is no clearer with omission of reward itself. While, as we noted, tasks such as extinction, conventional differential reinforcement of low rates (DRL) and discrimination reversal are sensitive to amygdala lesions, the closely related fixed interval and signalled DRL are not. (All of these tasks are sensitive to anxiolytic drugs.)

Finally, the results with novel stimuli are not consistent with a role for the amygdala in the aversive aspects of novelty. Amygdala lesions occasionally produce increases in ambulation in the open field but this measure is not unambiguously related to fear. They do not change freezing in the open field, they increase rather than decrease rearing (but see White and Weingarten 1976, who found a decrease in rearing when there was competition from eating), they do not consistently increase eating suppressed by a novel environment and they have no effect in the black–white box (Dringenberg *et al*., in press) or the plus maze (Treit and Menard 1997; Treit *et al.* 1998).

One suggestion which has been made is that 'the degree of arousal produced by the unconditioned stimulus, and not the aversive nature per se, determined the level of amygdala involvement' (Cahill and McGaugh 1990, cited by Davis 1992*b*, p285). While careful work would be required to substantiate this, on the evidence so far this could be the crucial feature which determines sensitivity to amygdala lesions in many cases. Particular care will need to be taken in assessing 'arousal' and its consequences, however, since it has been shown that, with simple Pavlovian appetitive conditioning, lesions of the central nucleus of the amygdala block *conditioning* of orienting responses previously elicited by the CS before conditioning occurred while not blocking conditioning of the approach responses previously elicited by the unconditioned stimulus (US) (Gallagher *et al.* 1990). Arousal, even if defined in terms of autonomic output, is always a slippery concept and an alternative view is that the amygdala is the site at which a 'wanting' component of reward is coded and that this is functionally and neurally separate from a 'liking' component (Berridge 1996).

Another alternative view is that the subcortical outputs of the amygdala activate target nuclei which not only control specific responses via descending connections but also (in the cases of the basal forebrain, substantia nigra, lateral dorsal tegmental nucleus, and pedunculopontine tegmental nucleus) control a variety of different types of attention via ascending connections to the diencephalon and telencephalon (Gallagher and Holland 1994; Gallagher and Chiba 1996).

We have talked so far as though the amygdala is an area which receives stimulus information, converts it into a 'threat' signal, and then distributes this signal to other areas which, on the basis of additional information, organize responses. This would certainly be consistent with the fact that, in humans, amygdala lesions impair the recognition of facial emotional expressions but not the identification of faces (Adolphs *et al*. 1994, 1995; see also Young *et al*. 1995, 1996) and that Bordi and Le Doux 'found some neurons in the rat amygdala that responded especially briskly to ultrasounds similar to the [rat's normal] warning calls . . . [suggesting that] the amygdala of all creatures may be prepared to respond to species-relevant cues' (Le Doux 1996, p. 254). However, if we view the amygdala, as we started, as one of the

higher levels of a system dedicated to *organizing* responses, we must qualify the generality of our picture. If its purpose is not threat analysis, in the most general sense, but the organization of active defensive responses to high levels of threat, this would account for the pattern of results which we have just considered. 'Arousal', then, would be simply a corollary of the type of threat requiring a *defensive* response. Likewise, while the lateral and basal nuclei of the amygdala might be characterized as threat detectors (albeit now tuned to those specific threats that require defensive reactions), the corticomedial complex is more likely to be characterized as a defence organizing system (which would be consistent with its extensive interconnectedness, and links with the thalamus and hypothalamus). Thus, Le Doux (1996, Figs 6–11, p. 160) shows the central nucleus as projecting to the PAG, lateral hypothalamus, paraventricular hypothalamus, and nucleus reticularis pontis caudalis to separately control the freezing, blood pressure, stress hormone, and startle components, respectively (see also Fig. 4.5 which shows Davis's similar view of amygdalar output).

In line with this view, Helmstetter (1992) has shown that if the amygdala (a mixture of central and basolateral sites) was inactivated with lidocaine either during pairing of a CS with shock, or during testing for conditioned fear after such pairing, or both, then lidocaine during pairing had negligible effects on subsequent testing, while lidocaine during testing had extensive effects which were not greatly different from lidocaine during both pairing and testing. This is 'consistent with other studies which have reported that when the central nucleus of the amygdala was lesioned in animals that had been trained with this structure intact, performance of the conditioned response was selectively abolished' (Helmstetter 1992, p. 1274; see Coleman-Mesches and McGaugh 1995, Coleman-Mesches *et al.* 1996 for evidence of lateralization of this effect; also Grillon and Davis 1995; Schneider *et al*. 1995). However, it is also clear that post-training lesions or inactivation may not have any effect if they are made sufficiently long after training (Liang *et al*. 1982; Parent and McGaugh 1994; and for similar results with inhibitory avoidance learning, Parent *et al*. 1995; but see also section on potentiated startle below) or if sufficiently extensive training is given before lesion (Parent *et al.* 1994). While amygdala lesions impair the acquisition of a secondary reinforcer value (e.g. Hatfield *et al*. 1996), Málková *et al.* (1997) found that learning of a visual discrimination based on previously acquired secondary reinforcement was unaffected by amygdala lesions but that devaluation of the secondary reinforcer by selective satiation was impaired. They suggested that 'the amygdala is necessary for learning the association between stimuli and the value of particular food rewards; however, the amygdala is not necessary for maintaining the value of secondary reinforcers, once they have been learned' (Málková *et al.* 1997, p. 6011). This proposed adjunctive role of the amygdala in the production of associative connections is, in a sense, the mirror image of the role we propose for the hippocampus in the suppression of associative connections—in both cases, once the 'emotional' business of acquisition is complete, 'habit' can be controlled by other structures.

A2.11 The amygdala, long-term potentiation, and memory

It should not be concluded from the above that the basal and lateral nuclei of the amygdala have no role to play in the conditioning (see, for example, Cousens and Otto, in press), as opposed to the expression of previously conditioned, defensive reactions. Indeed, Helmstetter himself suggests that 'the afferent pathway for CS information may terminate in the basolateral nuclear group while the normal performance of a number of conditioned

responses may depend on the efferent connections of the central nucleus' (Helmstetter 1992, p. 1275).

Particularly good evidence for the amygdala as the site for conditioning of defence is provided by studies on LTP (see Appendix 5).

LTP has been shown to occur in the amygdala (see Le Doux and Farb 1991, p. 145; Davis *et al.* 1994; Le Doux 1994, p. 36). Furthermore, LTP of the medial geniculate input to the lateral nucleus of the amygdala potentiates the field potential produced by a sound stimulus (Rogan and Le Doux 1995) while, conversely, fear conditioning potentiates CS-evoked responses in the lateral amygdala (Rogan *et al.* 1997*a*). More importantly for the linkage of these forms of LTP with the formation of CS–US associations:

> pretraining intra-amygdala infusion of NMDA receptor antagonists disrupted fear conditioning as measured by fear-potentiated startle, freezing, and inhibitory avoidance. On the other hand, pretest intra-amygdala infusion of NMDA antagonists did not significantly affect the performance of fear-potentiated startle or inhibitory avoidance, suggesting that amygdaloid NMDA receptors are involved in acquisition, but not in expression of conditioned fear. However, pre-test intra-amygdala infusion of [a] non-NMDA ionotropic receptor antagonist . . . impaired performance of inhibitory avoidance when the retention test was given one day after training. (M. Kim *et al.* 1993, p. 5; see also Rogan *et al.* 1997*b*; but see also McGaugh *et al.* 1992, especially pp. 444–445.)

Similar results have been obtained with second-order conditioning (Gewirtz and Davis 1997).

Consistent with a role for protein kinases in the later stages of establishment of LTP, kinase inhibitors injected into the amygdala immediately after avoidance training impaired retention (Walker and Gold 1994). However, there is also evidence that NMDA receptor antagonism of the basolateral amygdala impairs LTP in the dentate gyrus (Ikegaya *et al.* 1995*b*) so NMDA blockade of a particular site is not conclusive proof that LTP at that site mediates any resultant behavioural change.

To say that the amygdala is the site (via LTP) for the conditioning of defence is to say, in at least one sense, that the amygdala is the site of defensive memories. Until recently, it was thought that the amygdala made a much more extensive contribution to memory in general and, 'together with other medial temporal lobe structures such as the hippocampal formation and the entorhinal cortex, [was] necessary for accurate recognition memory as measured by the delayed nonmatching-to-sample task. [However,] it now seems more plausible to explain the effects of amygdala removal by aspiration in terms of the concomitant rhinal cortical damage' (Murray 1992, pp. 453, 468; see Murray *et al.* 1996 for a double dissociation of rhinal cortical effects on visual memory from amygdaloid effects on food preference). For example, NMDA antagonists injected into the amygdala impair inhibitory avoidance but have no effect on memory in the water maze (Liang *et al.* 1994) and benzodiazepines injected into the amygdala affect thigmotaxis in an empty water maze used as an open field but have no effects on spatial learning in the water maze once it is filled with water (McNamara and Skelton 1993). Even in the case of defensive reactions, it seems likely that the amygdala merely acts to support such reactions during the initial emotionally charged phase of acquisition and is not the site of more permanent storage (McGaugh *et al.* 1993) or may act to selectively enhance memory for emotionally charged information (particularly that which leads to the endogenous activation of beta receptors; Cahill *et al.* 1995, 1996). We discuss the role of the amygdala in memory in Chapter 8, but for the present we can paint a picture of the amygdala as a structure which is critical for the organization of defensive reactions: including, now, the linking (via LTP) of specific simple and complex stimuli to those

defensive reactions by conditioning. Nonetheless, we should also bear in mind that injections of NMDA antagonists into the amygdala can impair acquisition (while leaving intact performance) of certain appetitive tasks in the same way as it does aversive tasks (Burns *et al.* 1994).

The detailed mechanisms of conditioning which we have just reviewed are consistent with the view of Davis *et al.* (1994; see quotation above in section on the anatomy of the basal nucleus) that primarily cognitive information arrives in the lateral nucleus from the cortex, and an affective component is added by inputs to the basal nucleus from the parabrachial, insular cortical, and midline thalamic areas, all of which receive nociceptive input. Thus coincidence of CS input to the lateral nucleus with coincidence of US input to the basal nucleus would provide the basis for LTP and hence CS–US association.[7] Thus the primary location of the 'memory trace' would be at afferent synapses to the amygdala which provide primarily sensory information and these would be likely to be in the basolateral amygdala as opposed to central amygdala (Fanselow and Kim 1994; see Maren and Fanselow 1996 and Maren 1996 for recent overviews).

It should be noted, however, that if an *innate* fear stimulus were very complex it might well be processed in higher cortical areas and hence also provide input to the lateral nucleus. While this would muddy the clean division we have so far discerned between non-affective lateral nucleus information and affective basal nucleus information, it would not be problematic at the neural level. The current data show that LTP will cause 'innately neutral' stimuli arriving in the lateral nucleus to produce output from the basal nucleus which then results in defensive reactions. An innate fear stimulus of cortical origin would simply provide such supra-threshold input without the requirement for prior LTP. The evolution of such innate stimuli could be likened to the LTP process. Whereas LTP provides the basis for strengthening of the connection between an arbitrary stimulus and a defensive reaction, mutation can provide the basis for the selection of individuals progressively more prepared to form that connection for some specific stimulus. Thus, the functional distinction between 'neutral' and 'innate' stimuli arriving in the lateral nucleus is a labelling of two ends of a continuum of varying degrees of likelihood that some specific stimulus will elicit defence in the absence of prior LTP. It may be, also, that the requirement to process 'innate' stimuli provides the basis for the direct input to the basal nucleus from perirhinal as opposed to more unimodal sensory cortex.

A2.12 Amygdala—single-cell responses

Lesion studies have the major advantage of implicating a structure in some specific set of functions—but suffer from problems with non-specificity (e.g. through lesion of fibres en passage) and a lack of any indication as to how the function is performed. By contrast, single-unit studies allow one to be extremely precise about where a particular neuron is located and what its pattern of discharge is—but give no clue as to whether that discharge controls the current behaviour of the animal in any way. Combining the data from these two areas is, therefore, advantageous.

We will provide only a brief discussion of single-cell responses here taken, mainly, from two papers in the volume edited by Aggleton which we have used above. (Neither Le Doux nor Davis, our other two major sources so far, discuss single cells.) Rolls (1992) provides more of a synoptic overview than Ono and Nishijo (1992); however, we will start off with consideration of the latter so as to get some of the detailed flavour of this type of work.

The key problem with single-unit experiments is to determine why a neuron changes its firing rate. Suppose it does so as an animal reaches for a specific object: does the change in firing reflect some visual feature of the environment which is always perceived from a particular angle as the animal reaches for the object, or some specific visual feature of the object for which the animal is reaching; does it reflect the specific motivational state at the time of reaching; or does it reflect some (perhaps unobserved) aspect of motor adjustment during reaching? To attempt to settle these and related questions, it is usual to place the animal in a fairly restricted situation and then test each cell with a variety of stimuli and also, ideally, a variety of response requirements.

In the experiments described by Ono and Nishijo (1992), 'a monkey sat on a chair facing a panel containing shutters and an operant responding bar. Juice, water and saline were made available through a small spout with an electromagnetic valve. Weak electric shock could be applied between the two ear lobes' (Ono and Nishijo 1992, p. 168). The monkey could then be presented with a variety of objects of varying familiarity, with appetitive or aversive tasks, and with varying classical conditioning contingencies.

An immediate point to note is that, of nearly 600 neurons recorded from the amygdala, about half did not show any reaction to any of a wide variety of stimulus and contingency conditions. This argues for a degree of specificity of amygdaloid neurons in general, which is borne out by the pattern of results in the reactive neurons. Of the neurons which could be classified in detail, and which did show some reaction, about 20 per cent responded to visual stimuli only, about 10 per cent responded to auditory stimuli only, about 20 per cent responded during ingestion, about 10 per cent responded in a highly specific fashion to a particular object or stimulus, and about 40 per cent responded non-specifically to stimuli in a variety of modalities (see also Uwano *et al*. 1995). This last group of non-specific cells was found in the basal and corticomedial areas whereas the others were found in the lateral and basal areas. Thus, as we proceed more medially, the 'tuning' of the cells appears to become less specific.

This pattern is seen at lower as well as higher levels of analysis. For example, cells found in the lateral nucleus (which it will be remembered is largely a relay for incoming sensory information) reacted to novelty and signals of punishment but to neither reward, signals of reward, nor non-novel neutral stimuli. As we move medially to the basolateral nucleus, we find cells that react to reward, signals of reward, signals of punishment, novelty, to highly specific objects and stimuli, and to ingestion. This expansion of receptive field is best attributed to additional information arriving in the cortical (and perhaps thalamic) inputs to this area rather than to some transformation of the information available to the lateral nucleus.

In the case of cells which reacted to a novel stimulus, but which then habituated if that stimulus was neutral, 'all showed a reinstatement of responses when the stimulus was associated with electric shock' (Ono and Nishijo 1992, p. 175). Conversely, neurons which responded whenever a CS-food was presented showed decreased responding when the food was devalued by adding salt.

Unlike the studies reviewed by Rolls (1992), which we will consider shortly, Ono and Nishijo (1992, p. 184) found that 'there was not always a direct correlation between bar pressing and neural activity, while a direct link between neural activity in the amygdala and individual bar presses . . . was never observed.' They concluded that 'neural activity in the amygdala is not

directly related to either sensory inputs or to overt acts of the individual. Neuronal activity may, however, reflect motivational aspects of an animal's behavioural responses' (p. 184).

Rolls (1992) describes a range of studies which centre on the presentation to a monkey of visual stimuli which act as S+ or S– in visual discriminations. He concentrates on neurons which respond to the S+ for a reward. As with the neurons described by Ono and Nishijo, 'they did not respond to all visual stimuli that were positively reinforcing, and they often responded to one or more stimuli that were not positively reinforcing' (Rolls 1992, p. 147). Unlike the neurons described by Ono and Nishijo, the neurons did not change their responding when the visual discrimination was reversed and they now signalled delivery of saline rather than delivery of reward. Rolls suggests that this discrepancy results from the fact that in Ono and Nishijo's procedure the monkey need not fixate the stimulus once it has been devalued, whereas in the discrimination task it must fixate every stimulus. We will return to this point in a moment.

Rolls contrasts the relative invariance of amygdala responses with 'the responses of certain populations of neurons in the caudal orbitofrontal cortex and in a region to which it projects, the basal forebrain, which do show very rapid (in one or two trials) reversals of their responses in visual discrimination reversal tasks. . . . and it is this flexibility which it is suggested the orbitofrontal cortex adds to a more basic capacity which the amygdala implements for stimulus-reinforcement learning' (Rolls 1992, p. 149).

Let us look a little more closely at this suggestion that 'the amygdala implements . . . stimulus-reinforcement learning'. In the case of aversive conditioning, we have no problem. There is input to the amygdala from sensory areas; there is output from the amygdala to areas which control defence; LTP in the amygdala will simply link these two. With this scheme we can account both for a loss of aversive conditioning with amygdala lesions and for the presence of cells (particularly in the lateral nucleus) which respond to novel stimuli and stimuli which signal impending punishment (CS-Pun+). However, in the case of appetitive conditioning, the situation is not so clear. CS-Rew+ appear to activate only the basal and not the lateral nucleus and lesions of the amygdala do not impair unconditioned and conditioned appetitive reactions in the same way as they impair aversive ones. Indeed, where appetitive stimuli are used, it could be argued that the effects of amygdala lesions are on the aversive consequences of their removal not on their primary appetitive qualities.

This suggests that neurons in the amygdala respond to stimuli which have both positive and negative affective qualities but that it is only the latter which would normally (via LTP) come to produce an output from the amygdala to effector systems. But if this is so, why are there neurons which respond to positive affective stimuli at all? The problem arises from an apparent mismatch between the lesion and single-cell data. However, it will be remembered that even the lesion data did not support a clear appetitive/aversive distinction within the amygdala. In both cases, then, both appetitive and aversive stimuli may entrain the amygdala but there may be some critical feature of intensity of stimulus which is more common with aversive than appetitive stimuli, at least as these are presented in the laboratory.

A similar treatment appears to be accorded to 'neutral' stimuli. Bordi and Le Doux (1992) found that cells in the lateral amygdala which responded to simple auditory stimuli were often very broadly tuned but showed a preference for frequencies above 10 kHz with optimal responses in the region of 16 kHz, had high thresholds and, in more than half of the cases, showed extremely rapid habituation. All of these properties are consistent with an interest in

intense stimuli (see also Knuepfer *et al*. 1995) or ones which signal danger. With the exception of habituation, they appear to derive directly from the properties of the thalamic afferent cells (Bordi and Le Doux 1994).

On this view, some cells in the amygdala react to positive and/or negative reinforcing stimuli and 'neutral high intensity' stimuli whether or not the amygdala is currently controlling behaviour. At sufficient levels of input activation, coupled with output activation of, for example, defensive systems, LTP supplies the basis for conditioning. The stimuli subsequently have the capacity to elicit the appropriate (e.g. defensive) reaction.[8] In this context, it is interesting that some cells show delay-related firing (Nakamura *et al.* 1992) which could provide a basis for subsequent conditioning and which may reflect interaction with working memory areas of prefrontal cortex (see next appendix).

We should make explicit, here, something we have implicitly assumed, namely that quite complex mechanisms elsewhere have actually classified stimuli as potentially threatening or rewarding and have then passed them on to the amygdala for further consideration and action. Thus, a crude (but potentially multimodal; Bordi and Le Doux 1994) signal arrives from the thalamus and is then confirmed (or otherwise) by subsequent signals arising from the cortex (Le Doux 1994). In both the cortical and the thalamic case it is only selected stimuli which are transmitted to the amygdala, not copies of the entire sensory input.

This makes sense of the reactions of amygdala neurons to novel and familiar stimuli. As described by Ono and Nishijo (1992, see above), a stimulus can initially produce a response in an amygdala neuron, then habituate, then respond again when the stimulus is associated with shock (although, as Rolls has noted, this could be the result of changes in fixation of the stimuli involved). Likewise, Rolls (1992, pp. 152–4) describes cells which, in a recognition memory task, respond more when a stimulus is novel than at its second presentation, but where the response to the second presentation increases, eventually to the 'novel' level, as an increasing number of other stimuli are interposed between the first and second presentation. In each of these cases we can see perceptual systems of the brain passing to the amygdala only information which is likely to be of importance.

It should be noted that the extreme responsiveness of amygdala neurons to certain novel stimuli is not inconsistent with the lack of any major effect of amygdala lesions on responses to novelty. The amygdala receives a novel stimulus because such stimuli could well require high-level action (e.g. defensive responses). However, LTP, and hence subsequent functional output from the amygdala, will only occur if the novel stimulus is associated with some event which unconditionally activates output from the amygdala (e.g. a defensive reaction).

A final category of responses reviewed by Rolls is that to faces. Some neurons in the amygdala respond to faces with some apparent selection for identity. 'It is suggested that the tameness of the Klüver–Bucy syndrome, and the inability of amygdalectomized monkeys to interact normally in a social group arises because of damage to a system specialized for processing faces' (Rolls 1992, p. 154). From our present perspective, this reactivity to faces, like that to other stimuli, will occur because of their potential to provide intense significant stimuli and they do not need to be treated as a special case. Indeed, in humans, the facial processing which is affected by amygdala lesions is of emotional expression, leaving perception of identity intact (Adolphs *et al*. 1994). While faces might seem to be unusually complicated stimuli, it is worth noting that the innate (or indeed learned) reaction to a snake as posited by Le Doux (1994) also requires extremely complicated processing.

When considering such data it is tempting to see cellular correlates as reflecting very high-level information processing by a structure. To bring us back to earth, we should remind ourselves that amygdala cells very frequently fire in anticipation of blood pressure and heart rate changes (Schulz *et al*. 1986; see also Langhorst *et al*. 1987; Lambertz *et al*. 1995) and injections of GABA anatagonists into the basolateral amygdala can cause significant increases in heart rate and blood pressure (Sanders and Shekhar 1991). The apparently complex coding of the cells could, then, reflect no more than their activation, from elsewhere, as a relay for the production of autonomic responses (see Kapp *et al*. 1991 for a model of autonomic control by the amygdala).

A2.13 The defence system—integration

As detailed in Table 6.1 (Chapter 6), defensive systems appear to be organized hierarchically. The PAG is at a low level and is concerned with the release of a suite of motor programmes (e.g. undirected escape, aggression) which are designed to remove the animal from harm as quickly as possible and with the minimum of analytical finesse. Thus the PAG can provide an ultra-quick, ultra-dirty motor solution to problems of defence. The medial hypothalamus is at the next level and can be viewed as performing essentially the same function (e.g. directed or learned escape, but now inhibiting aggression), but where there is more time, more flexibility in terms of options, and where conditioning can influence responding. Despite being (or indeed because of being) at the level above the PAG, the medial hypothalamus can be viewed as operating via connections with the PAG (some excitatory, some inhibitory). The amygdala is at the next level again. Here complex conditioning is possible (e.g. avoidance) and, it appears, the systems controlled by the structure can include not only the defence system proper but other systems which deal, for example, with the omission of reward and certain aspects of appetitive stimuli as well. Like the hypothalamus, the amygdala will have both excitatory and inhibitory connections with lower levels. Thus, reward omission per se (like pain) will elicit aggression, and we can presume that this is mediated by an excitatory input from the amygdala to the PAG; but where avoidance of reward omission is more appropriate, the PAG will tend to be inhibited and higher levels of the system will control behaviour. The final level, in terms of active avoidance involving more complex stimuli, both learned and innate, is the anterior cingulate cortex, which we will consider in the next appendix.

The picture we have presented of threat analysis by the amygdala (following closely Le Doux 1994) is of a structure which receives, from the higher levels of sensory cortex (and from the lower levels of subcortical sensory afferent systems), information about the presence of threatening stimuli, about novel stimuli, and about previously neutral stimuli which are occurring in the context of threat. Aversive conditioning would then occur in the amygdala through LTP of synapses linking incoming, previously ineffective, stimuli with the defence control system. The output from the amygdala would then result in output from the hypothalamus and the PAG if the simplest types of autonomic and motor response are sufficient or from the more general motor programming areas of the cortex and basal ganglia if more flexible avoidance is required. Note that the associative nature of LTP makes it almost essential that the amygdala should control, via innate stimuli, reactions that can become conditioned to neutral stimuli.

The aversive reactions mediated by the amygdala include those consequent on the omission of reward, and it also appears that the amygdala mediates purely appetitive reactions where the stimulus intensity is sufficiently high. Thus, animals and humans can show self-stimulation in the amygdala and humans can report pleasure with amygdala stimulation.

Based on this, Kesner (1992, p. 383; see also Le Doux 1993) has argued 'that the amygdala is critically involved in the encoding of emotional (positive and negative) attributes (internal context) of memory . . . [an] idea [which] is an extension of earlier theoretical notions that the amygdala is involved in the interpretation and integration of reinforcing stimuli, serves as a reinforcement register, or mediates stimulus-reinforcement associations.' However, we would broaden Kesner's view to include the innate encoding of such information as well as providing the basis for memory. This, or some rule like it, could account for an involvement of the amygdala in both food selection and mate selection.

The requirements of these different responses vary, and their interaction is coordinated by interactions between the different levels of the defence system and by the ascending serotonergic system which we will consider in more detail in Appendix 10. An important point, to which we will return at the end of the book, is that the hierarchical organization of the system in terms of sophistication of analysis and control nonetheless means that the lowest level of our analysis, the PAG, can be viewed as the main output station for primary defensive reactions arising at all levels (e.g. Blanchard *et al*. 1981; see also the specific model presented by Fanselow 1991).

The contribution of the amygdala to defence can be pictured by combining the ideas of Davis (1992*a*) and Le Doux (1994, 1996). The amygdala receives relatively low-grade, but affectively labelled, information about sensory inputs from the thalamus. It receives (with somewhat greater delay) extremely highly processed, cognitive rather than affective, information about the same sensory inputs from the highest levels of unimodal and polymodal cortex. Novel sensory stimuli are sent to the lateral nucleus of the amygdala but, unless they are associated with affective input, they rapidly habituate. Learned avoidance depends on the pairing of a CS (arriving in the lateral nucleus) with a US, arriving in the basal nucleus, and on the resultant LTP of the connection between the CS and the UR. This is the paradigm case of Pavlovian stimulus substitution. In principle, specific biologically prepared stimuli could operate in a similar fashion with their initial input being sufficient, even in the absence of LTP, to produce a UR. This latter possibility also allows for the progressive phylogenetic acquisition of an innate fear stimulus by the progressive genetic strengthening of initially 'neutral' inputs until they become capable of unconditionally generating the relevant responses.

The various outputs of the central nucleus of the amygdala then control the different components of different URs and CRs. Fear (in the highest sense) would, on this view, result from activity in the basal nucleus of the amygdala and this could lead to: (a) defensive reactions via the subcortical outflow from the central nucleus; (b) the adjustment of learned avoidance via the outflow from the basal nucleus to the striatum; (c) anxiety via the outflow to the septo-hippocampal system; and (d) focusing of attention and increased negative cognitive bias via the recursive outflow from the basal nucleus to all levels of the visual cortex and other sensory systems both directly and via the basal forebrain cholinergic system.

This relatively simple picture needs to be qualified in three ways. First, the amygdala appears to be involved not only in fear processing, but also in the processing of frustration, sex, and at least some aspects of food and drug preference. On the other hand, it may not be involved in the processing of all aversive stimuli. We may accept, as a working hypothesis, that the key aspect of stimuli which activate the amygdala is that they produce a high level of physiological arousal. Thus, highly arousing positively reinforcing stimuli will activate the amygdala while relatively non-arousing negatively reinforcing stimuli will not. The

superficial selectivity of the amygdala for negative, and particularly threat, stimuli would then be attributed to the fact that these are the commonest highly arousing stimuli with which the animal has to deal, especially in a laboratory setting. This view is not dissimilar from the idea that the amygdala is involved in controlling attention to motivationally significant stimuli (Gallagher and Holland 1994; Gallagher and Chiba 1996).

Second, while we have so far made a case for the amygdala being solely involved in the processing of 'pure' fear stimuli, and while this might argue for any involvement in anxiety being indirect (i.e. the result of combining fear with some conflicting source of motivation), we have nonetheless seen evidence that at least some of the actions of the anxiolytic drugs are the result of a direct action of these drugs on receptors in the amygdala. The most important case of this kind, theoretically speaking, is that of fear-potentiated startle. The role of the amygdala in this phenomenon, and in its abolition by anxiolytic drugs, is discussed in detail in Chapters 6 (Section 6.3.7) and 11 (Section 11.3).

Third, in all of this we have discussed the contribution of the areas concerned to defence, and there is a good case to be made for them being parts of a much more generalized affective motor system (Holstege 1991, 1992).

There are a number of reasons for not identifying anxiety entirely with the operations of the amygdala. First, it allows a neurological hierarchy to largely match the psychological and functional hierarchy which we described in Chapters 2 and 3. Second, as we have already mentioned, and will consider in detail in the following appendices, there are other brain systems on which the anxiolytic drugs act directly and which negate any hope that the action of the drugs can be understood in terms of action at a single brain nucleus (even in the amygdala there appear to be several distinct sites of action). Third, we present a range of arguments, particularly in Appendix 8, that the septo-hippocampal system is at least as important for anxiety as the amygdala and probably more important for anxiolytic action. The amygdaloid action of the anxiolytic drugs, then, can be seen as operating on some of the common functional outputs of fear and anxiety, rather than because the amygdala is central to anxiety itself. For example, while there are changes in benzodiazepine receptor binding in the hippocampus and frontal cortex in response to novelty and cat odour, there are no such changes in the amygdala (Hogg and File 1994).

In the present appendix we have dealt with brain defence systems which provide a necessary precursor to some types of anxiety but which are only partially involved in anxiety itself. In Appendix 3 we will discuss the role of the frontal and cingulate cortices, which can be viewed as the highest levels of the defence system. Finally, in the remaining appendices, we will take a detailed look at the septo-hippocampal system and its aminergic afferents.

References

Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, **372**, 669–72.

Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. R. (1995). Fear and the human amygdala. *The Journal of Neuroscience*, **15**, 5879–91.

Aggleton, J. P. (1992). *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* Wiley-Liss, New York.

Aggleton, J. P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends in Neuroscience*, **16**, 328–33.

Albert, D. J., Walsh, M. L., and Jonik, R. H. (1993). Aggression in humans: what is its biological foundation? *Neuroscience and Biobehavioral Reviews*, **17**, 405–25.

Amaral, D. G., Price, J. L., Pitkänen, A., and Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 1–66. Wiley-Liss.

Audi, E. A., de Oliveira, R. M. W., and Graeff, F. G. (1991). Microinjection of propranolol into the dorsal periaqueductal gray causes an anxiolytic effect in the elevated plus-maze antagonized by ritanserin. *Psychopharmacology (Berlin)*, **105**, 553–7.

Bacon, S. J., Headlam, A. J. N., Gabbott, P. L. A., and Smith, A. D. (1996). Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. *Brain Research*, **720**, 211–19.

Bandler, R. and Carrive, P. (1988). Integrated defence reaction elicited by excitatory amino acid microinjection in the midbrain periaqueductal grey region of the unrestrained cat. *Brain Research*, **439**, 95–106.

Bandler, R. and Shipley, M. T. (1994). Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? *Trends in Neuroscience*, **17**, 379–89.

Beck, C. H. M. and Fibiger, H. C. (1995). Conditioned fear-induced changes in behavior and in the expression of the immediate early gene *c-fos*: with and without diazepam pretreatment. *The Journal of Neuroscience*, **15**, 709–20.

Bernardis, L. L. and Bellinger, L. L. (1987). The dorsomedial hypothalamic nucleus revisited: 1986 update. *Brain Research Reviews*, **12**, 321–81.

Bernardis, L. L. and Bellinger, L. L. (1993). The lateral hypothalamic area revisited: neuroanatomy, body weight regulation, neuroendocrinology and metabolism. *Neuroscience and Biobehavioral Reviews*, **17**, 141–93.

Berridge, K. C. (1996). Food reward: brain substrates of wanting and liking. *Neuroscience and Biobehavioral Reviews*, **20**, 1–25.

Blanchard, D. C., Williams, G., Lee, E. M. C., and Blanchard, R. J. (1981). Taming of wild *Rattus norvegicus* by lesions of the mesencephalic central gray. *Physiological Psychology*, **9**, 157–63.

Bordi, F. and Le Doux, J. E. (1992). Sensory tuning beyond the sensory system: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. *The Journal of Neuroscience*, **12**, 2493–503.

Bordi, F. and Le Doux, J. E. (1994). Response properties of single units in areas of rat auditory thalamus that project to the amygdala. I. Acoustic discharge patterns and frequency receptive fields. *Experimental Brain Research*, **98**, 261–74.

Borlongan, C. V. and Watanabe, S. (1994). Failure to discriminate conspecifics in amygdaloid-lesioned mice. *Pharmacology, Biochemistry and Behavior*, **48**, 677–80.

Bragin, E. O., Yeliseeva, Z. V., Vasilenko, G. F., Meizerov, E. E., Chuvin, B. T., and Durinyan, R. A. (1984). Cortical projections to the periaqueductal grey in the cat: a retrograde horseradish peroxidase study. *Neuroscience Letters*, **51**, 271–5.

Brandão, M. L., Melo, L. L., and Cardoso, S. H. (1993). Mechanisms of defense in the inferior colliculus. *Behavioural Brain Research*, **58**, 49–55.

Brinley-Reed, M., Mascagni, F., and McDonald, A. J. (1995). Synaptology of prefrontal cortical projections to the basolateral amygdala: an electron microscopic study in the rat. *Neuroscience Letters*, **202**, 45–8.

Brown, E. E. and Fibiger, H. C. (1993). Differential effects of excitotoxic lesions of the amygdala on cocaine-induced conditioned locomotion and conditioned place preference. *Psychopharmacology (Berlin)*, **113**, 123–30.

Burns, L. H., Everitt, B. J., and Robbins, T. W. (1994). Intra-amygdala infusion of the *N*-methyl-d-aspartate receptor antagonist AP5 impairs acquisition but not performance of discriminated approach to an appetitive CS. *Behavioral and Neural Biology*, **61**, 242–50.

Cahill, L., Babinsky, R., Markowitsch, H. J., and McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature*, **377**, 295–6.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., *et al.* (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences of the United States of America*, **93**, 8016–21.

Callaway, C. W., Hakan, R. L., and Henriksen, S. J. (1991). Distribution of amygdala input to the nucleus accumbens septi: an electrophysiological investigation. *Journal of Neural Transmission*, **83**, 215–25.

Canteras, N. S., Simerly, R. B., and Swanson, L. W. (1994). Organization of projections from the ventromedial nucleus of the hypothalamus: a *Phaseolus vulgaris*–leucoagglutinin study in the rat. *The Journal of Comparative Neurology*, **348**, 41–79.

Canteras, N. S., Simerly, R. B., and Swanson, L. W. (1995). Organization of projections from the medial nucleus of the amygdala: a PHAL study in the rat. *The Journal of Comparative Neurology*, **360**, 213–45.

Canteras, N. S., Chiavegatto, S., Do Valle, L. E. R., and Swanson, L. W. (1997). Severe reduction of rat defensive behavior to a predator by discrete hypothalamic chemical lesions. *Brain Research Bulletin*, **44**, 297–305.

Carrive, P. (1993). The periaqueductal gray and defensive behavior: functional representation and neuronal organisation. *Behavioural Brain Research*, **58**, 27–47.

Carrive, P. and Bandler, R. (1991). Viscerotopic organization of neurons subserving hypotensive reactions within the midbrain periaqueductal grey: a correlative functional and anatomical study. *Brain Research*, **541**, 206–15.

Carrive, P., Leung, P., Harris, J., and Paxinos, G. (1997). Conditioned fear to context is associated with increased fos expression in the caudal ventrolateral region of the midbrain periaqueductal gray. *Neuroscience*, **78**, 165–77.

Coleman-Mesches, K., and McGaugh, J. L. (1995). Differential effects of pretraining inactivation of the right or left amygdala on retention of inhibitory avoidance training. *Behavioral Neuroscience*, **109**, 642–7.

Coleman-Mesches, K., Salinas, J. A., and McGaugh, J. L. (1996). Unilateral amygdala inactivation after training attenuates memory for reduced reward. *Behavioural Brain Research*, **77**, 175–80.

Cousens, G. and Otto, T. (1998). Both pre-and posttraining excitotoxic lesions of the basolateral amygdala abolish the expression of olfactory and contextual fear conditioning. *Behavioral Neuroscience*, **112**, 1092-1103.

Crovetti, R., Lucchetti, F., Mancia, M., Mariotti, M., Porrini, M., Spinnler, P., *et al.* (1995). Food intake after amygdaloid lesion in rats. *Nutrition Research*, **15**, 565–70.

Da Costa Gomez, T. M., and Behbehani, M. M. (1995). An electrophysiological characterization of the projection from the central nucleus of the amygdala to the periaqueductal gray of the rat: the role of opioid receptors. *Brain Research*, **689**, 21–31.

Davis, M. (1992*a*). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, **15**, 353–75.

Davis, M. (1992*b*). The role of the amygdala in conditioned fear. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 255–305. Wiley-Liss.

Davis, M., Rainnie, D., and Cassell, M. (1994). Neurotransmission in the rat amygdala related to fear and anxiety. *Trends in Neuroscience*, **17**, 208–14.

Decker, M. W., Curzon, P., and Brioni, J. D. (1995). Influence of separate and combined septal and amygdala lesions on memory, acoustic startle, anxiety, and locomotor activity in rats. *Neurobiology of Learning and Memory*, **64**, 156–68.

Desmedt, A., Garcia, R., and Jaffard, R. (1998). Differential modulation of changes in hippocampal–septal synaptic excitability by the amygdala as a function of either elemental or contextual fear conditioning in mice. *The Journal of Neuroscience*, **18**, 480–7.

DiMicco, J. A. and Monroe, A. J. (1996). Stimulation of metabotropic glutamate receptors in the dorsomedial hypothalamus elevates heart rate in rats. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, **270**, R1115–21.

DiMicco, J. A., Stotz-Potter, E. H., Monroe, A. J., and Morin, S. M. (1996). Role of the dorsomedial hypothalamus in the cardiovascular response to stress. *Clinical and Experimental Pharmacology and Physiology*, **23**, 171–6.

Dringenberg, H.C., Kornelsen, R.A., Pacelli, R., Petersen, K., and Vanderwolf, C.H. (1998). Effects of amygdaloid lesions, hippocampal lesions, and buspirone on black-white exploration and food carrying in rats. *Behavioral Brain Research*, **96**, 161-172.

Dunn, J. D. and Williams, T. J. (1995). Cardiovascular responses to electrical stimulation of the bed nucleus of the stria terminalis. *The Journal of Comparative Neurology*, **352**, 227–34.

Fallon, J. H. and Ciofi, P. (1992). Distribution of monoamines within the amygdala. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 97–114. Wiley-Liss.

Fanselow, M. S. (1991). The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety. In *The midbrain periaqueductal gray matter* (ed. A. Depaulis and R. Bandler), pp. 151–73. Plenum Press, New York.

Fanselow, M. S. and Kim, J. J. (1994). Acquisition of contextual Pavlovian fear conditioning is blocked by application of an NMDA receptor antagonist d,l-2-amino-5-phosphonovaleric acid to the basolateral amygdala. *Behavioral Neuroscience*, **108**, 210–12.

Fendt, M., Koch, M., and Schnitzler, H.-U. (1994). Lesions of the central gray block the sensitization of the acoustic startle response in rats. *Brain Research*, **661**, 163–73.

Fendt, M., Koch, M., and Schnitzler, H.-U. (1996). Lesions of the central gray block conditioned fear as measured with the potentiated startle paradigm. *Behavioural Brain Research*, **74**, 127–34.

Ferry, B., Sandner, G., and Di Scala, G. (1995). Neuroanatomical and functional specificity of the basolateral amygdaloid nucleus in taste-potentiated odor aversion. *Neurobiology of Learning and Memory*, **64**, 169–80.

Fox, R. J. and Sorenson, C. A. (1994). Bilateral lesions of the amygdala attenuate analgesia induced by diverse environmental challenges. *Brain Research*, **648**, 215–21.

Fulton, J. F. (1932). New horizons in physiology and medicine: the hypothalamus and visceral mechanisms. *New England Journal of Medicine*, **207**, 60–95.

Gallagher, M. and Chiba, A. A. (1996). The amygdala and emotion. *Current Opinion in Neurobiology*, **6**, 221–7.

Gallagher, M. and Holland, P. C. (1994). The amygdala complex: multiple roles in associative learning and attention. *Proceedings of the National Academy of Sciences of the United States of America*, **91**, 11771–6.

Gallagher, M., Graham, P. W., and Holland, P.C. (1990). The amygdala central nucleus and appetitive pavlovian conditioning: lesions impair one class of conditioned behaviour. *The Journal of Neuroscience*, **10**, 1906–11.

Gallo, M., Roldan, G., and Bures, J. (1992). Differential involvement of gustatory insular cortex and amygdala in the acquisition and retrieval of conditioned taste aversion in rats. *Behavioural Brain Research*, **52**, 91–7.

Gewirtz, J. C. and Davis, M. (1997). Second-order fear conditioning prevented by blocking NMDA receptors in amygdala. *Nature*, **388**, 471–4.

Gören, Z., Aslan, N., Berkman, K., Oktay, S., and Onat, F. (1996). The role of amygdala and hypothalamus in $GABA_A$ antagonist bicuculline-induced cardiovascular responses in conscious rats. *Brain Research*, **722**, 118–24.

Gorman, J. M., Liebowitz, M. R., Fyer, A. J., and Stein, J. (1989). A neuroanatomical hypothesis for panic disorder. *American Journal of Psychiatry*, **146**, 148–61.

Graeff, F.G. (1994). Neuroanatomy and neurotransmitter regulation of defensive behaviors and related emotions in mammals. *Brazilian Journal of Medical and Biological Research*, **27**, 811-829.

Grillon, C. and Davis, M. (1995). Acoustic startle and anticipatory anxiety in humans: effects of monaural right and left ear stimulation. *Psychophysiology*, **32**, 155–61.

Harris, J.A., & Westbrook, R.F. (1995). Effects of benzodiazepine microinjection into the amygdala or periaqueductal gray on the expression of conditioned fear and hypoalgesia in rats. *Behavioral Neuroscience*, **109**, 295-304.

Harvey, A. T., Moore, H., Lucot, J. B., and Hennesey, M. B. (1994). Monoamine activity in anterior hypothalamus of guinea pig pups separated from their mothers. *Behavioral Neuroscience*, **108**, 171–6.

Hatfield, T. and Gallagher, M. (1995). Taste-potentiated odor conditioning: impairment produced by infusion of an *N*-methyl-d-aspartate antagonist into basolateral amygdala. *Behavioral Neuroscience*, **109**, 663–8.

Hatfield, T., Han, J.-S., Conley, M., Gallagher, M., and Holland, P. (1996). Neurotoxic lesions of basolateral, but not central, amygdala interfere with pavlovian second-order conditioning and reinforcer devaluation effects. *The Journal of Neuroscience*, **16**, 5256–65.

Heckers, S. and Mesulam, M.-M. (1994). Two types of cholinergic projections to the rat amygdala. *Neuroscience*, **60**, 383–97.

Helmstetter, F. J. (1992). Contribution of the amygdala to learning and performance of conditional fear. *Physiology and Behavior*, **51**, 1271–6.

Helmstetter, F. J. and Tershner, S. A. (1994). Lesions of the periaqueductal gray and rostral ventromedial medulla disrupt antinociceptive but not cardiovascular aversive conditional responses. *The Journal of Neuroscience*, **14**, 7099–108.

Henke, P. G. (1977). Dissociation of the frustration effect and the partial reinforcement extinction effect after limbic lesions in rats. *Journal of Comparative and Physiological Psychology*, **91**, 1032–8.

Herbert, H. and Saper, C. B. (1992). Organization of medullary adrenergic and noradrenergic projections to the periaqueductal gray matter in the rat. *The Journal of Comparative Neurology*, **315**, 34–52.

Hogg, S. and File, S. E. (1994). Regional differences in rat benzodiazepine binding in response to novelty and cat odour. *Neuropharmacology*, **33**, 865–8.

Holstege, G. (1989). Anatomical study of the final common pathway for vocalization in the cat. *The Journal of Comparative Neurology*, **284**, 242–52.

Holstege, G. (1991). Descending motor pathways and the spinal motor system: limbic and non-limbic components. In *Progress in brain research* (ed. G. Holstege), pp. 307–421. Elsevier Science.

Holstege, G. (1992). The emotional motor system. *European Journal of Morphology*, **30**, 67–79.

Ikegaya, Y., Saito, H., and Abe, K. (1994). Attenuated hippocampal long-term potentiation in basolateral amygdala-lesioned rats. *Brain Research*, **656**, 157–64.

Ikegaya, Y., Abe, K., Saito, H., and Nishiyama, N. (1995*a*). Medial amygdala enhances synaptic transmission and synaptic plasticity in the dentate gyrus of rats in vivo. *Journal of Neurophysiology*, **74**, 2201–3.

Ikegaya, Y., Saito, H., and Abe, K. (1995*b*). Amygdala *N*-methyl-d-aspartate receptors participate in the induction of long-term potentiation in the dentate gyrus in vivo. *Neuroscience Letters*, **192**, 193–6.

Inglefield, J. R., Schwarzkopf, S. B., and Kellogg, C. K. (1994). Alterations in behavioral responses to stressors following excitotoxin lesions of dorsomedial hypothalamic regions. *Brain Research*, **633**, 151–61.

Iwata, J., Le Doux, J. E., and Reis, D. J. (1986). Destruction of intrinsic neurons in the lateral hypothalamus disrupts the classical conditioning of autonomic but not behavioral emotional responses in the rat. *Brain Research*, **368**, 161–6.

Jenck, F., Moreau, J. L., and Martin, J. R. (1995). Dorsal periaqueductal gray-induced aversion as a simulation of panic anxiety: elements of face and predictive validity. *Psychiatry Research*, **57**, 181–91.

Johnson, L. R., Aylward, R. L. M., and Totterdell, S. (1994*a*). Synaptic organization of the amygdalar input to the nucleus accumbens in the rat. In *The basal ganglia* (ed. G. Percheron), pp. 109–14. Plenum Press, New York.

Johnson, L. R., Aylward, R. L. M., Hussain, Z., and Totterdell, S. (1994*b*). Input from the amygdala to the rat nucleus accumbens: its relationship with tyrosine hydroxylase immunoreactivity and identified neurons. *Neuroscience*, **61**, 851–65.

Jurgens, U. (1994). The role of the periaqueductal grey in vocal behaviour. *Behavioural Brain Research*, **62**, 107–17.

Kalsbeek, A., Drijfhout, W.J., Westernik, B.H.C., Van Heerikhuize, J.J., Van der Woude, T.P., Van der Vliet, J., & Buijs, R.M. (1996). GABA receptors in the region of the dorsomedial hypothalamus of rats are implicated in the

control of melatonin and corticosterone release. *Neuroendocrinology*, **63**, 69-78.

Kapp, B. S., Markgraf, C. G., Wilson, A., Pascoe, J. P., and Supple, W. F. (1991). Contributions of the amygdala and anatomically-related structures to the acquisition and expression of aversively conditioned responses. In *Current topics in animal learning: brain, emotion and cognition* (ed. L. Dachowski and C. F. Flaherty), pp. 311–46. Erlbaum, Hillsdale, NJ.

Kapp, B. S., Supple, W. F., Jr., and Whalen, P. J. (1994). Effects of electrical stimulation of the amygdaloid central nucleus on neocortical arousal in the rabbit. *Behavioral Neuroscience*, **108**, 81–93.

Kesner, R. P. (1992). Learning and memory in rats with an emphasis on the role of the amygdala. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 379–99. Wiley-Liss.

Kesner, R. P. and Williams, J. M. (1995). Memory for magnitude of reinforcement: dissociation between the amygdala and hippocampus. *Neurobiology of Learning and Memory*, **64**, 237–44.

Kesner, R. P., Walser, R. D., and Winzenried, G. (1989). Central but not basolateral amygdala mediates memory for positive affective experiences. *Behavioural Brain Research*, **33**, 189–95.

Kim, J. J., Rison, R. A., and Fanselow, M. S. (1993). Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. *Behavioral Neuroscience*, **107**, 1093–8.

Kim, M., Campeau, S., Falls, W. A., and Davis, M. (1993). Rapid communication: infusion of the non-NMDA receptor antagonist CNQX into the amygdala blocks the expression of fear-potentiated startle. *Behavioral and Neural Biology*, **59**, 5–8.

King, B. M., Kass, J. M., Neville, K. L., Sam, H., Tatford, A. C., III, and Zansler, C. A. (1993). Abnormal weight gain in rats with amygdaloid lesions. *Physiology and Behavior*, **54**, 467–70.

Kirkpatrick, B., Kim, J. W., and Insel, T. R. (1994*a*). Limbic system *fos* expression associated with paternal behavior. *Brain Research*, **658**, 112–18.

Kirkpatrick, B., Carter, C. S., Newman, S. W., and Insel, T. R. (1994*b*). Axon-sparing lesions of the medial nucleus of the amygdala decrease affiliative behaviors in the prairie vole (*Microtus ochrogaster*): behavioral and anatomical specificity. *Behavioral Neuroscience*, **108**, 501–13.

Kirouac, G. J. and Ganguly, P. K. (1995). Topographical organization in the nucleus accumbens of afferents from the basolateral amygdala and efferents to the lateral hypothalamus. *Neuroscience*, **67**, 625–30.

Knuepfer, M. M., Eismann, A., Schütze, I., Stumpf, H., and Stock, G. (1995). Responses of single neurons in amygdala to interoceptive and exteroceptive stimuli in conscious cats. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, **268**, R666–75.

Kondo, Y. (1992). Lesions of the medial amygdala produce severe impairment of copulatory behavior in sexually inexperienced male rats. *Physiology and Behavior*, **51**, 939–43.

Kondo, Y. and Arai, Y. (1995). Functional association between the medial amygdala and the medial preoptic area in regulation of mating behavior in the male rat. *Physiology and Behavior*, **57**, 69–73.

La Bar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., and Phelps, E.A. (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron*, **20**, 937-945.

Lambertz, M., Schulz, G., and Langhorst, P. (1995). Cardiac rhythmic patterns in neuronal activity related to the firing rate of the neurons: II. Amygdala neurons of cats. *Journal of the Autonomic Nervous System*, **51**, 165–73.

Langhorst, P., Lambertz, M., Schulz, G., and Stock, G. (1987). Role played by amygdala complex and common brainstem system in integration of somatomotor and autonomic components of behaviour. In *Organization of the autonomic nervous system: central and peripheral mechanisms* (ed. F. R. Calaresu), pp. 347–61. Alan R Liss.

Le Doux, J. E. (1992). Emotion and the amygdala. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 339–51. Wiley-Liss.

Le Doux, J. E. (1993). Emotional memory systems in the brain. *Behavioural Brain Research*, **58**, 69–79.

Le Doux, J. E. (1994). Emotion, memory and the brain. *Scientific American*, **270**, 50–9.

Le Doux, J. E. (1995). Emotion: clues from the brain. *Annual Review of Psychology*, **46**, 209–35.

Le Doux, J. E. (1996). *The emotional brain.* Simon and Schuster, New York.

Le Doux, J. E. and Farb, C. R. (1991). Neurons of the acoustic thalamus that project to the amygdala contain glutamate. *Neuroscience Letters*, **134**, 145–9.

Le Doux, J. E., Iwata, J., Cicchetti, P., and Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditional fear. *The Journal of Neuroscience*, **8**, 2517–29.

Liang, K. C., McGaugh, J. L., Martinez, J. L., Jr., Jensen, R. A., Vasquez, B. J., and Messing, R. B. (1982). Post-training amygdaloid lesions impair retention of an inhibitory avoidance response. *Behavioural Brain Research*, **4**, 237–49.

Liang, K. C., Hon, W., and Davis, M. (1994). Pre- and posttraining infusion of *N*-methyl-d-aspartate receptor antagonists into the amygdala impair memory in an inhibitory avoidance task. *Behavioral Neuroscience*, **108**, 241–53.

Liebman, J. M., Mayer, D. J., and Liebeskind, J. C. (1970). Mesencephalic central gray lesions and fear-motivated behavior in rats. *Brain Research*, **23**, 353–70.

Lovick, T. A. (1993). The periaqueductal gray–rostral medulla connection in the defence reaction: efferent pathways and descending control mechanisms. *Behavioural Brain Research*, **58**, 19–25.

Málková, L., Gaffan, D., and Murray, E. A. (1997). Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *The Journal of Neuroscience*, **17**, 6011–20.

Malsbury, C. W. and McKay, K. (1994). Neurotrophic effects of testosterone on the medial nucleus of the amygdala in adult male rats. *Journal of Neuroendocrinology*, **6**, 57–69.

Maren, S. (1996). Synaptic transmission and plasticity in the amygdala—an emerging physiology of fear conditioning circuits. *Molecular Neurobiology*, **13**, 1–22.

Maren, S. and Fanselow, M. S. (1995). Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation in vivo. *The Journal of Neuroscience*, **15**, 7548–64.

Maren, S. and Fanselow, M. S. (1996). The amygdala and fear conditioning: has the nut been cracked? *Neuron*, **16**, 237–40.

Mateus, M.G., Nogueira, R.L., Carobez, A.P., Graeff, F.G., and Guimares, F.S. (1994). Anxiolytic effect of glycine antagonists microinjected into the dorsal periaqueductal grey. *Psychopharmacology (Berl)*, **113**, 565-569.

McDonald, A. J. and Mascagni, F. (1996). Cortico-cortical and cortico-amygdaloid projections of the rat occipital cortex: a *Phaseolus vulgaris* leucoagglutinin study. *Neuroscience*, **71**, 37–54.

McDonald, A. J., Mascagni, F., and Guo, L. (1996). Projections of the medial and lateral prefrontal cortices to the amygdala: a *Phaseolus vulgaris* leucoagglutinin study in the rat. *Neuroscience*, **71**, 55–75.

McDonald, R. J. and White, N. M. (1995). Information acquired by the hippocampus interferes with acquisition of the amygdala-based conditioned-cue preference in the rat. *Hippocampus*, **5**, 189–97.

McGaugh, J. L., Introini-Collison, I. B., Cahill, L., Kim, M., and Liang, K. C. (1992). Involvement of the amygdala in neuromodulatory influences on memory storage. In *The amygdala* (ed. J. P. Aggleton), pp. 431–51. Wiley-Liss, New York.

McGaugh, J. L., Introini-Collison, I. B., Cahill, L. F., Castellano, C., Dalmaz, C., Parent, M. B., *et al.* (1993). Neuromodulatory systems and memory storage: role of the amygdala. *Behavioural Brain Research*, **58**, 81–90.

McNamara, R. K. and Skelton, R. W. (1993). Effects of intracranial infusions of chlordiazepoxide on spatial learning in the Morris water maze. I. Neuroanatomical specificity. *Behavioural Brain Research*, **59**, 175–91.

McNaughton, N. (1989). *Biology and emotion.* Cambridge University Press.

Mello, L. E. A. M., Tan, A. M., and Finch, D. M. (1992). Convergence of projections from the rat hippocampal formation, medial geniculate and basal forebrain onto single amygdaloid neurons: an in vivo extra- and intracellular electrophysiological study. *Brain Research*, **587**, 24–40.

Milani, H. and Graeff, F. G. (1987). GABA–benzodiazepine modulation of aversion in the medial hypothalamus of the rat. *Pharmacology, Biochemistry and Behavior*, **28**, 21–7.

Minano, F. J., Meneres Sancho, M. S., Sancibrian, M., Salinas, P., and Myers, R. D. (1992). GABAA receptors in the amygdala: role in feeding in fasted and satiated rats. *Brain Research*, **586**, 104–10.

Minerbo, G., Albeck, D., Goldberg, E., Lindberg, T., Nakari, M., Martinez, C., *et al.* (1994). Activity of peptidergic neurons in the amygdala during sexual behavior in the male rat. *Experimental Brain Research*, **97**, 444–50.

Mumby, D. G., Pinel, J. P. J., Kornecook, T. J., Shen, M. J., and Redila, V. A. (1995). Memory deficits following lesions of hippocampus or amygdala in rat: assessment by an object–memory test battery. *Psychobiology*, **23**, 26–36.

Murray, E. A. (1992). Medial temporal lobe structures contributing to recognition memory: the amygdaloid complex versus the rhinal cortex. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 431–51. Wiley-Liss.

Murray, E. A., Gaffan, E. A., and Flint, R. W., Jr. (1996). Anterior rhinal cortex and amygdala: dissociation of their contributions to memory and food preference in rhesus monkeys. *Behavioral Neuroscience*, **110**, 30–42.

Nakamura, K., Mikami, A., and Kubota, K. (1992). Activity of single neurons in the monkey amygdala during performance of a visual discrimination task. *Journal of Neurophysiology*, **67**, 1447–63.

Narita, K., Nishihara, M., and Takahashi, M. (1994). Concomitant regulation of running activity and metabolic change by the ventromedial nucleus of the hypothalamus. *Brain Research*, **642**, 290–6.

Numan, M. (1994). A neural circuitry analysis of maternal behavior in the rat. *Acta Paediatrica*, **83** (Suppl. 397**)**, 19–28.

Ono, T. and Nishijo, H. (1992). Neurophysiological basis of the Kluver–Bucy syndrome: responses of monkey amygdaloid neurons to biologically significant objects. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 167–90. Wiley-Liss.

Parent, M. B. and McGaugh, J. L. (1994). Posttraining infusion of lidocaine into the amygdala basolateral complex impairs retention of inhibitory avoidance training. *Brain Research*, **661**, 97–103.

Parent, M. B., West, M., and McGaugh, J. L. (1994). Memory of rats with amygdala lesions induced 30 days after footshock-motivated escape training reflects degree of original training. *Behavioral Neuroscience*, **108**, 1080–7.

Parent, M. B., Quirarte, G. L., Cahill, L., and McGaugh, J. L. (1995). Spared retention of inhibitory avoidance learning after posttraining amygdala lesions. *Behavioral Neuroscience*, **109**, 803–7.

Paré, D. and Gaudreau, H. (1996). Projection cells and interneurons of the lateral and basolateral amygdala: distinct firing patterns and differential relation to theta and delta rhythms in conscious cats. *The Journal of Neuroscience*, **16**, 3334–50.

Paré, D. and Smith, Y. (1994). GABAergic projection from the intercalated cell masses of the amygdala to the basal forebrain in cats. *The Journal of Comparative Neurology*, **344**, 33–49.

Paré, D., Smith, Y., and Paré, J. F. (1995*a*). Intra-amygdaloid projections of the basolateral and basomedial nuclei in the cat: *Phaseolus vulgaris*–leucoagglutinin anterograde tracing at the light and electron microscopic level. *Neuroscience*, **69**, 567–83.

Paré, D., Pape, H. C., and Dong, J. M. (1995*b*). Bursting and oscillating neurons of the cat basolateral amygdaloid complex in vivo: electrophysiological properties and morphological features. *Journal of Neurophysiology*, **74**, 1179–91.

Petrovich, G. D., Risold, P. Y., and Swanson, L. W. (1996). Organization of projections from the basomedial nucleus of the amygdala: a PHAL study in the rat. *The Journal of Comparative Neurology*, **374**, 387–420.

Pitkänen, A. and Amaral, D. G. (1994). The distribution of GABAergic cells, fibers, and terminals in the monkey amygdaloid complex: an immunohistochemical and *in situ* hybridization study. *The Journal of Neuroscience*, **14**, 2200–24.

Pitkänen, A., Stefanacci, L., Farb, C. R., Go, G.-G., Le Doux, J. E., and Amaral, D. G. (1995). Intrinsic connections of the rat amygdaloid complex: projections originating in the lateral nucleus. *The Journal of Comparative Neurology*, **356**, 288–310.

Pitkänen, A., Savander, V., and Le Doux, J. E. (1997). Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. *Trends in Neuroscience*, **20**, 517–23.

Raffaele, K. C. and Olton, D. S. (1988). Hippocampal and amygdaloid involvement in working memory for nonspatial stimuli. *Behavioral Neuroscience*, **102**, 349–355.

Redgrave, P. and Dean, P. (1991). Does the PAG learn about emergencies from the superior colliculus? In *The midbrain periaqueductal gray matter* (ed. A. Depaulis and R. Bandler), pp. 199–209. Plenum Press, New York.

Rizvi, T. A., Ennis, M., Behbehani, M. M., and Shipley, M. T. (1991). Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: topography and reciprocity. *The Journal of Comparative Neurology*, **303**, 121–31.

Roeling, T. A. P., Veening, J. G., Kruk, M. R., Peters, J. P. W., Vermelis, M. E. J., and Nieuwenhuys, R. (1994). Efferent connections of the hypothalamic 'aggression area' in the rat. *Neuroscience*, **59**, 1001–24.

Rogan, M. T. and Le Doux, J. E. (1995). LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. *Neuron*, **15**, 127–36.

Rogan, M.T., Stäubli, U.V., and Le Doux, J.E. (1997*a*). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature*, **390**, 604-607

Rogan, M. T., Stäubli, U. V., and Le Doux, J. E. (1997*b*). AMPA receptor facilitation accelerates fear learning without altering the level of conditioned fear acquired. *The Journal of Neuroscience*, **17**, 5928–35.

Rolls, E. T. (1992). Neurophysiology and functions of the primate amygdala. In *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction* (ed. J. P. Aggleton), pp. 143–65. Wiley-Liss.

Romanski, L. M. and Le Doux, J. E. (1993). Information cascade from primary auditory cortex to the amygdala: corticocortical and corticoamygdaloid projections of temporal cortex in the rat. *Cerebral Cortex*, **3**, 515–32.

Salinas, J. A., Parent, M. B., and McGaugh, J. L. (1996). Ibotenic acid lesions of the amygdala basolateral complex or central nucleus differentially effect the response to reductions in reward. *Brain Research*, **742**, 283–93.

Sanders, S. K. and Shekhar, A. (1991). Blockade of GABAA receptors in the region of the anterior basolateral amygdala of rats elicits increases in heart rate and blood pressure. *Brain Research*, **576**, 101–10.

Sandner, G., Oberling, P., Silveira, M. C. L., Di Scala, G., Rocha, B., Bagri, A., *et al.* (1993). What brain structures are active during emotions? Effects of brain stimulation elicited aversion on c-*fos* immunoreactivity and behavior. *Behavioural Brain Research*, **58**, 9–18.

Saper, C. B. (1985). Organization of cerebral cortical afferent systems in the rat. II. Hypothalamocortical projections. *The Journal of Comparative Neurology*, **237**, 21–46.

Sarter, M. and Markowitsch, H. J. (1985). The involvement of the amygdala in learning and memory: a critical review with emphasis on anatomical relations. *Behavioral Neuroscience*, **99**, 342–80.

Savander, V., Go, C. G., Le Doux, J. E., and Pitkänen, A. (1995). Intrinsic connections of the rat amygdaloid complex: projections originating in the basal nucleus. *The Journal of Comparative Neurology*, **361**, 345–68.

Savander, V., Go, C. G., Le Doux, J. E., and Pitkänen, A. (1996). Intrinsic connections of the rat amygdaloid complex: projections originating in the accessory basal nucleus. *The Journal of Comparative Neurology*, **374**, 291–313.

Savander, V., Le Doux, J. E., and Pitkänen, A. (1997*a*). Interamygdaloid projections of the basal and accessory basal nuclei of the rat amygdaloid complex. *Neuroscience*, **76**, 725–35.

Savander, V., Miettinen, R., Le Doux, J. E., and Pitkänen, A. (1997*b*). Lateral nucleus of the rat amygdala is reciprocally connected with basal and accessory basal nuclei: a light and electron microscopic study. *Neuroscience*, **77**, 767–81.

Schmued, L. C. (1994). Diagonal ventral forebrain continuum has overlapping telencephalic inputs and brainstem outputs which may represent loci for limbic/autonomic integration. *Brain Research*, **667**, 175–91.

Schneider, F., Gur, R. E., Mozley, L. H., Smith, R. J., Mozley, P. D., Censits, D. M., *et al.* (1995). Mood effects on limbic blood flow correlate with emotional self-rating: a PET study with oxygen-15 labeled water. *Psychiatry Research: Neuroimaging Section*, **61**, 265–83.

Schubert, K., Shaikh, M. B., and Siegel, A. (1996). NMDA receptors in the midbrain periaqueductal gray mediate hypothalamically evoked hissing behavior in the cat. *Brain Research*, **726**, 80–90.

Schulkin, J. (1994). Melancholic depression and the hormones of adversity: a role for the amygdala. *Current Directions in Psychological Science*, **3**, 41–4.

Schulkin, J., McEwen, B. S., and Gold, P. W. (1994). Allostasis, amygdala, and anticipatory angst. *Neuroscience and Biobehavioral Reviews*, **18**, 385–96.

Schulz, G., Lambertz, M., Stock, G., and Langhorst, G. (1986). Neuronal activity in the amygdala related to somatomotor and vegetative components of behaviour in cats. *Journal of the Autonomic Nervous System, Suppl.*, 639–48.

Seeley, R. J., Galaverna, O., Schulkin, J., Epstein, A. N., and Grill, H. J. (1993). Lesions of the central nucleus of the amygdala. II: Effects on intraoral NaCl intake. *Behavioural Brain Research*, **59**, 19–25.

Shaikh, M. B., Schubert, K., and Siegel, A. (1994). Basal amygdaloid facilitation of midbrain periaqueductal gray elicited defensive rage behavior in the cat is mediated through NMDA receptors. *Brain Research*, **635**, 187–95.

Shekhar, A. (1993). GABA receptors in the region of the dorsomedial hypothalamus of rats regulate anxiety in the elevated plus-maze test. I. Behavioral measures. *Brain Research*, **627**, 9–16.

Shekhar, A. (1994). Effects of treatment with imipramine and clonazepam on an animal model of panic disorder. *Biological Psychiatry*, **36**, 748–58.

Shekhar, A., Sims, L. S., and Bowsher, R. R. (1993). GABA receptors in the region of the dorsomedial hypothalamus of rats regulate anxiety in the elevated plus-maze test. II. Physiological measures. *Brain Research*, **627**, 17–24.

Shekhar, A., Katner, J. S., Rusche, W. P., Sajdyk, T. J., and Simon, J. R. (1994). Fear-potentiated startle elevates catecholamine levels in the dorsomedial hypothalamus of rats. *Pharmacology, Biochemistry and Behavior*, **48**, 525–9.

Shinonaga, Y., Takada, M., and Mizuno, N. (1994). Direct projections from the non-laminated divisions of the medial geniculate nucleus to the temporal polar cortex and amygdala in the cat. *The Journal of Comparative Neurology*, **340**, 405–26.

Shipley, M. T., Ennis, M., Rizvi, T. A., and Behbehani, M. M. (1991). Topographical specificity of forebrain inputs to the midbrain periaqueductal gray: evidence for discrete longitudinally organized input columns. In *The midbrain periaqueductal gray matter* (ed. A. Depaulis and R. Bandler), pp. 417–48. Plenum Press, New York.

Silveira, M. C. L. and Graeff, F. G. (1992). Defense reaction elicited by microinjection of kainic acid into the medial hypothalamus of the rat: antagonism by a GABA A receptor agonist. *Behavioral and Neural Biology*, **57**, 226–32.

Silveira, M. C. L., Sandner, G., Di Scala, G., and Graeff, F. G. (1995). C-*fos* immunoreactivity in the brain following electrical or chemical stimulation of the medial hypothalamus of freely moving rats. *Brain Research*, **674**, 265–74.

Smith, Y. and Paré, D. (1994). Intra-amygdaloid projections of the lateral nucleus in the cat: PHA-L anterograde labeling combined with postembedding GABA and glutamate immunocytochemistry. *The Journal of Comparative Neurology*, **342**, 232–48.

Stefanacci, L., Suzuki, W. A., and Amaral, D. G. (1996). Organization of connections between the amygdaloid complex and the perirhinal and parahippocampal cortices in macaque monkeys. *The Journal of Comparative Neurology*, **375**, 552–82.

Stotz-Potter, E. H., Willis, L. R., and DiMicco, J. A. (1996). Muscimol acts in dorsomedial but not paraventricular hypothalamic nucleus to suppress cardiovascular effects of stress. *The Journal of Neuroscience*, **16**, 1173–9.

Tranel, D. and Hyman, T. (1990). Neuropsychological correlates of bilateral amygdala damage. *Archives of Neurology*, **47**, 349–55.

Treit, D. and Menard, J. (1997). Dissociations among the anxiolytic effects of septal, hippocampal, and amygdaloid lesions. *Behavioral Neuroscience*, **111**, 653–8.

Treit, D., Aujla, H., and Menard, J. (1998). Does the bed nucleus of the stria terminalis mediate fear behaviors? *Behavioral Neuroscience*, **112**, 379–86.

Uwano, T., Nishijo, H., Ono, T., and Tamura, R. (1995). Neuronal responsiveness to various sensory stimuli, and associative learning in the rat amygdala. *Neuroscience*, **68**, 339–61.

Van Erp, A. M. M., Kruk, M. R., Meelis, W., and Veening, J. G. (1993). Periaqueductal gray lesions do not affect grooming, induced electrically in the hypothalamic paraventricular area in the rat. *Behavioural Brain Research*, **59**, 95–101.

Vertes, R. P. (1992). PHA-L analysis of projections from the supramammillary nucleus in the rat. *The Journal of Comparative Neurology*, **326**, 595–622.

Walker, D. L. and Gold, P. E. (1994). Intra-amygdala kinase inhibitors disrupt retention of a learned avoidance response in rats. *Neuroscience Letters*, **176**, 255–8.

Weiner, I., Tarrasch, R., and Feldon, J. (1996). Basolateral amygdala lesions do not disrupt latent inhibition. *Behavioural Brain Research*, **72**, 73–81.

White, N. M. and Weingarten, H. (1976). Effects of amygdala lesions on exploration by rats. *Physiology and Behavior*, **17**, 73–9.

Wright, C. I., Beijer, A. V. J., and Groenewegen, H. J. (1996). Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. *The Journal of Neuroscience*, **16**, 1877–93.

Yamamoto, T., Shimura, T., Sako, N., Yasoshima, Y., and Sakai, N. (1994). Neural substrates for conditioned taste aversion in the rat. *Behavioural Brain Research*, **65**, 123–37.

Yamamoto, T., Fujimoto, Y., Shimura, T., and Sakai, N. (1995). Conditioned taste aversion in rats with excitotoxic brain lesions. *Neuroscience Research*, **22**, 31–49.

Yasoshima, Y., Shimura, T., and Yamamoto, T. (1995). Single unit responses of the amygdala after conditioned taste aversion in conscious rats. *Neuroreport*, **6**, 2424–8.

Young, A. W., Aggleton, J. P., Hellawell, D. J., Johnson, M., Broks, P., and Hanley, J. R. (1995). Face processing impairments after amygdalotomy. *Brain*, **118**, 15–24.

Young, A. W., Hellawell, D. J., Van De Wal, C., and Johnson, M. (1996). Facial expression processing after amygdalotomy. *Neuropsychologia*, **34**, 31–9.

Zhang, S. P., Bandler, R., and Carrive, P. (1990). Flight and immobility evoked by excitatory amino acid microinjection within distinct parts of the subtentorial midbrain periaqueductal gray of the cat. *Brain Research*, **520**, 73–82.

Notes

1. Absence of attack-like behaviours would be difficult to explain if the PAG stimulation were *activating* fight–flight–freeze circuits. However, brain stimulation, and natural stimuli, are much more likely to *release* tonic inhibition from such circuits. This allows *conditional* appearance of any specific one of a set of concurrently released behaviours depending on available sensory stimuli (McNaughton 1989, Chapter 2). This interpretation is greatly strengthened by the fact that unilateral injections result in defensive reactions only to contralaterally presented stimuli (Bandler and Carrive 1988).

2. For a detailed review of the lateral hypothalamic area, including its relations with the dorso- and ventromedial hypothalamic areas, see Bernardis and Bellinger 1993; for an earlier detailed review of the DMH see Bernardis and 1987; for evidence of a role for the DMH in the control of diurnal variations in melatonin and corticosterone see Kalsbeek *et al*. 1996.

3. It is also the opposite of what would be obtained with the intermediate hypothalamic 'aggression area' which, interestingly, does not project to the DMH but does project to the lateral septum (Roeling *et al*. 1994).

4. The MH does not appear to have extensive projections to the non-limbic isocortex (Saper 1985).

5. Our amalgamation here departs, for the sake of simplicity, from that of Amaral *et al*. (1992); see also Paré *et al.* (1995*a*) on the distinction between basolateral and basomedial nuclei; Savander *et al*. (1995) on the division of the basal nucleus into magnocellular, intermediate, and parvicellular portions; and Petrovich *et al.* (1996) on the division of the basomedial nucleus into quite distinct anterior and posterior parts.

6. It may be that this input from the lateral nucleus is the basis for the diminution in perforant path-dentate gyrus long-term potentiation seen after basolateral amygdala lesions (Ikegaya *et al.* 1994).

7. The input to the lateral nucleus from the thalamus, at least, appears to be glutamatergic (Le Doux and Farb 1991) and so not only could strong input from this pathway result in LTP of other inputs but it might well also undergo LTP itself.

8. No special neurophysiological mechanisms are required to support this idea—LTP only occurs when there is sufficient activation of any input. However, both increased and decreased responses can be observed as a result of conditioning and the relative balance between these can vary between different areas of the amygdala (Yasoshima *et al.* 1995) and possibilities such as LTP of input to inhibitory interneurons must be taken into account.

==========
==========
==========