2 The neuropsychology of fear and anxiety: a foundation for Reinforcement Sensitivity Theory

Neil McNaughton and Philip J. Corr

Personality factors, as normally studied, are sources of variation that are stable over time and that derive from underlying properties of an individual more than current changes in their environment. They account for behavioural differences between individuals presented with identical environments that show consistent patterns within that individual across time. As such, an ultimate goal of personality research must be to identify the relatively static biological variables that determine the superficial factor structure evident in behaviour and other measures. This is not to deny the importance of the environment in controlling personality. But, to produce consistent long-term effects, environmental influences must be mediated by, and instantiated in, biological systems. Biology can also be viewed as more fundamental in that environmental events (such as an impact to the front of the head) have permanent effects on personality not in relation to the external parameters of the event (such as the force of impact) but rather in relation to the precise extent of change the event induces in the brain.

Those interested in individual variation in the tendency to neurotic disorders have been particularly inclined to theorize in terms of either the real or the conceptual nervous system. Pavlov saw variation in the response of his dogs to both traumatic and everyday events as arising from the 'Strength of the Nervous System' – a purely theoretical construct, albeit with a consistent behavioural structure (Gray 1964, 1967). H.J. Eysenck (1944, 1947) used factor analysis of a medical checklist of neurotic symptoms in a clinical population to identify and then develop, in the normal population, the constructs of Extraversion and Neuroticism. He then linked these constructs to conditionability of neural connections and so to the development of neurotic behaviour. The most extensive exegesis has been that of Gray. He (Gray 1970) first proposed an alternative theoretical account of the genesis of the *same* neurotic

behaviour as Eysenck starting with a modest rotation of Eysenck's original factor axes. This allowed him to attribute neurotic disorder to a factor of punishment sensitivity, which he then linked (Gray 1976, 1982), via his theory of a 'Behavioural Inhibition System' (BIS), to a detailed neural architecture.

Gray's theory of the BIS is primarily an account of state changes. His personality theory (from which modern Reinforcement Sensitivity Theory (RST), derives) assumes that the entire BIS is subject to global modulation that accounts for trait/personality variation. As a result the predictions of his personality theory are strongly related to the details of his account of state changes. This chapter[1] describes recent refinements of the state aspects of the BIS at both the conceptual and neural levels (Gray and McNaughton 2000; McNaughton and Corr 2004). Much of the revised theory is clarification and repackaging of the old theory. But some changes that are minor at the state level represent significant alterations to the foundations of RST. They demand the reformulation of experimental tests of RST in terms of the revised theory. For research purposes, this revised theory replaces the old theory. The specific implications of these alterations for theories of personality are dealt with in a separate chapter (see Corr and McNaughton, chapter 5). The key differences and similarities between Gray's (1982) neuropsychological theory and the updated theory are summarized in Table 2.1 The justification for, and main details of, the updated theory are presented below.

A 'state' level analysis of defence

To understand large-scale, long-term ('trait') modulation of neural systems it is first necessary to have at least an approximate idea of the functioning of those systems on shorter ('state') timescales. It is in these state variations that the structure and processes of neuropsychological systems are most evident. Neural level analysis also requires, as a precursor, some degree of coherent conceptualization of the structure of behaviour. We need to know what the theory is attempting to explain. This section, therefore, deals with some critical psychological constructs derived largely from Gray (1982) and Gray and McNaughton (2000).

Reward and punishment

Substantive affective events can be viewed as falling into just two distinct major classes: positive and negative (Gray 1975, 1982; Gray

[1] This chapter is based substantially on McNaughton and Corr (2004).

Table 2.1 *Comparison of original and updated theories of the neuropsychology of anxiety (bold items represent significant changes)*

Concept	Gray (1982)	Gray and McNaughton 2000 McNaughton and Corr 2004
Fear and anxiety		
Fear (FFFS)	Fight-Flight	Fight-Flight-**Freeze**
Anxiety (BIS)	behavioural inhibition increased arousal, attention, exploration	behavioural inhibition increased arousal, attention, **risk assessment**
Fear/Anxiety	unconditioned/ conditioned	**threat avoidance/threat approach**
The Behavioural Inhibition System		
BIS defined by	anxiolytic action	anxiolytic action
Inputs to BIS	stated ad hoc	**derived from conflict/threat approach**
Conflict	activates BIS, includes: approach-approach approach-avoidance avoidance-avoidance	activates BIS, includes: approach-approach approach-avoidance avoidance-avoidance
Neuropsychology		
Anxiolytic drugs	act via theta rhythm	act via theta rhythm, **and amygdala and other areas**
Anxiety (cognition)	via hippocampus	via hippocampus + **other areas**
Anxiety (arousal)	via hippocampus	**via amygdala**
Overall system	unitary	**distributed**
Personality/Disorders		
Neurotic disorders	unitary control	separate control
Neurotic personality	punishment sensitivity (anxiety)	punishment sensitivity (**fear** + anxiety)
Trait anxiety	= neurotic personality	# **neurotic personality**

and McNaughton 2000). Rewards and punishments are the obvious exemplars of positive and negative events, respectively. But, importantly for human experiments, the absence of an expected positive event is functionally the same as the presence of a negative event and vice versa (Gray 1975). Omission of expected reward is thus punishing. Similarly, the absence of an expected negative event is functionally the same as the presence of a positive event. Omission of punishment is rewarding.

This creates a significant problem for human testing. Given the right context, a 'non-event' is motivationally significant. If we wish to measure pure reward sensitivity, then we must do so in paradigms that

do not involve omission of reward as a consequence of error. As will become clear below, we must particularly guard against equivalent levels of reward and punishment as these generate conflict, with additional consequences. Since conditional stimuli acquire secondary reinforcement value, we must take care also that 'neutral' stimuli are actually neutral for each person tested and do not have some previously acquired value.

Fear and anxiety: defensive direction

The revised theory treats fear and anxiety as not only quite distinct but also, in a sense, as opposites. A categorical separation of fear from anxiety as classes of defensive responses has been demonstrated by Robert and Caroline Blanchard (Blanchard and Blanchard 1988, 1989, 1990; Blanchard, Griebel, Henrie and Blanchard 1997).

The Blanchards used 'ethoexperimental analysis' of the innate reactions of rats to cats to determine the functions of specific classes of behaviour. One class of behaviours was elicited by the immediate presence of a predator. This class could clearly be attributed to a state of fear. The behaviours, grouped into the class on purely ethological grounds, were sensitive to panicolytic drugs but not to drugs that are anxiolytic but not panicolytic (Blanchard, Griebel, Henrie and Blanchard 1997). This is consistent with the insensitivity to anxiolytic drugs of active avoidance in a wide variety of species and of phobia in humans (Sartory, MacDonald and Gray 1990). A second, quite distinct, class of behaviours (including 'risk assessment') was elicited by the potential presence of a predator. This class of behaviours was sensitive to anxiolytic drugs. Both functionally and pharmacologically this class was distinct from the behaviours attributed to fear and could be attributed to a state of anxiety.

The Blanchards distinguished their classes of behaviour (and so their attribution of fear or anxiety) in terms of whether the behaviours were elicited by an actual or a potential predator. However, similar behaviours, and similar differential drug sensitivities, in more formal learning experiments (Gray 1977) show that fear is more the result of a requirement to avoid danger than of the immediacy (or certainty) of threat. (Of course, with strong dangers avoidance will be mandatory.) Likewise, anxiety is more the result of a requirement to approach danger than of the potentiality (or uncertainty) of it. Fear operates when leaving a dangerous situation (active avoidance), anxiety when entering it (e.g., cautious 'risk assessment' approach behaviour) or withholding entrance

(passive avoidance). The critical factor distinguishing fear from anxiety can, then, be called 'defensive direction'.

While they are directionally opposed, there is, nonetheless, considerable functional overlap between the generation of fear and anxiety. In particular, anxiety involves modulation of pre-existing fear (or frustration). Also, in natural situations, there is a strong correlation between uncertainty of threat and the need to approach the source of potential threat. This correlation, we argue, has resulted in a greater elaboration of the neural control of fear relative to anxiety at lower levels of the neural hierarchy and a relatively greater elaboration of anxiety relative to fear at the higher levels.

On this view, there is a sharp (functional, behavioural and pharmacological) distinction between fear and anxiety. Fear has the function of moving the animal away from danger. It involves fight-flight-freezing, and is *insensitive* to anxiolytic drugs. When in an approach-avoidance conflict situation, anxiety has the function of moving the animal toward danger. It involves inhibition of prepotent behaviours, increased risk assessment and defensive quiescence. All these manifestations of the core state of anxiety are *sensitive* to anxiolytic drugs. Unlike Gray's 1982 theory (and many others) this distinction between fear and anxiety does not depend on the conditioned or unconditioned nature of stimuli used.

This is one crucial difference (Table 2.1) between Gray's original (1976, 1982) formulation and the revised theory (Gray and McNaughton 2000; McNaughton and Corr 2004). In the old theory, anxiety (activation of the BIS) resulted primarily from *conditioned* aversive stimuli. Strong unconditioned stimuli would lead to fear and so avoidance behaviour. But, almost by definition, anxiety would only be induced by potential threat (i.e., the conditioned signal, or warning, of threat). However, anxiety could also, according to Gray (1982), be induced by a rag-bag of 'innate fears' – confusingly included on an ad hoc basis. The new theory resolves this confusion and is explicit as to *exactly* what leads to fear and anxiety, respectively. With both innate and conditioned stimuli, it is defensive direction. In the old theory, fear played a pivotal role. It was necessary for aversive conditioning: it provided the central state to which neutral stimuli got associated. However, the personality theory, and so RST personality research, emphasized the BIS. The new theory suggests that fear is equally important in relation to personality and, in particular, the clinical consequences of extreme personality. In particular, the neurotic disorders are equally divided between what the theory defines as fears and what the theory defines as anxieties.

Conflict

We have just defined anxiety in terms of defensive approach. However, embedded in this idea is the more fundamental concept of conflict – because one only approaches a threat if there is some positive, conflicting, reason that makes avoidance inappropriate. Although this chapter focuses largely on defensive approach and defensive avoidance, it should be noted that the BIS is held to be engaged with any type of conflict, including approach-approach conflict (see Gray and McNaughton 2000, Appendix 1 and Appendix 8). Thus, defensive approach (approach to a threat) is paradigmatic in having clear appetitive and aversive components that are easily identified. But threats are not the only sources of aversion and avoidance that we experience. Indeed, in modern society omission of an expected reward (frustration) is a much more common source of aversion and stress than stimuli that produce pain or the threat of death. The theory holds that anxiety results from conflicts between competing available goals, whatever their source. The classic form of such conflict (Miller 1944; Kimble 1961; Gray 1987), and the most familiar for those studying anxiety, is approach-avoidance (McNaughton 2001). However, in principle, approach-approach and avoidance-avoidance conflicts would involve activation of the same system and have essentially the same effects as approach-avoidance. Approach-approach conflict (e.g., which of two competing job offers to take) is not likely normally to generate high levels of anxiety. The aversive component of the conflict rests in the frustration that could result from the relative loss incurred if the wrong choice is made and this will usually be small. However, it seems likely that the chronic stress that can, over a long period, precipitate anxiety disorders will, in developed societies, often reflect such conflicts more than classic approach-avoidance. According to this view, this process underlies the vague sense of dissatisfaction that is said to pervade advanced capitalist societies: we are spoiled for choice!

It is also important to realize that the presence or absence of conflict is something determined at least as much by the participant as by the experimenter. It is not necessary or sufficient that there be a nominal conflict in the formal description of a paradigm. Conflict can arise between an unexpected innate tendency and a conditioned response. Conversely, there may be no real conflict even in what is formally passive avoidance – which might be thought to be the quintessence of behavioural inhibition. For example (Okaichi and Okaichi 1994), rats with septo-hippocampal lesions showed no passive avoidance deficit in a running wheel *in which there was little spontaneous running* – unless they

were first trained on a contrary active avoidance response. In refutation of radical behaviourism, it is the internal state of the animal that is as much to blame for conflict as the formal arrangement of environmental contingencies (see chapter 3).[2]

Defensive distance

A simple two-dimensional categorization of all defensive behaviour (and neurotic disorders) is provided by the superimposition on the categorical dimension of defensive direction (i.e., approach threat or avoid threat) of a graded dimension 'defensive distance', as defined by the Blanchards. For a particular individual in a particular situation, defensive distance equates with real distance. But, in a more dangerous situation, a greater real distance will be required to achieve the same defensive distance. Likewise, in the same situation, but with a braver individual, a smaller real distance will be required to achieve the same defensive distance. Defensive distance thus operationalizes an internal cognitive construct of intensity of perceived threat. It is a dimension controlling the type of defensive behaviour observed. We will later show that it is the conceptual basis of individual differences in sensitivity to aversive reinforcement.

In the case of defensive avoidance, the smallest defensive distances result in explosive attack, intermediate defensive distances result in freezing and flight, and very great defensive distances result in normal non-defensive behaviour (Figure 2.1A). In humans, the psychological state at very small defensive distance would be labelled panic. The commonly associated cognition in panic 'I'm going to die' would seem homologous to whatever cognitions can be attributed to a rat when it is nose-to-nose with a cat (one of the situations analysed by the Blanchards). Intermediate defensive distances can be equated with phobic avoidance.

With the opposite direction, defensive approach (Figure 2.1B), defensive quiescence occurs at the closest defensive distances (and, in rats, can be distinguished from freezing only by minor postural features and its sensitivity to anxiolytic drugs). At intermediate distances, risk assessment behaviour occurs and, at very great distances, defensive behaviour disappears and normal pre-threat behaviour reappears.[3]

[2] Diehard radical behaviourists would argue that these 'fictional' internal states are themselves the product of prior reinforcement history. For our analysis, this argument is irrelevant because the influence of such history must be instantiated in brain systems – and we know that variations in the neural functioning of these systems should influence both the sensitivity and reactivity to reinforcement and thus to their long-term influence.

[3] It might be thought that a highly active BIS would be associated with greater goal conflict resolution, thus BIS active individuals should be superior conflict resolvers. However, it

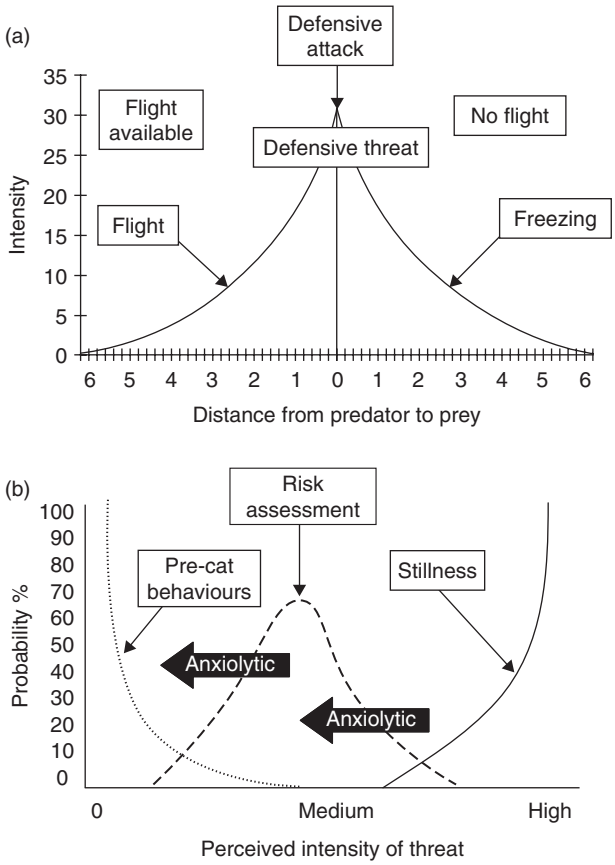

Figure 2.1 The relationship between defensive distance and behaviour. A. For defensive avoidance, from Blanchard and Blanchard (1990). B. For defensive approach. The grey arrows represent a fixed change in defensive distance produced by anxiolytic drugs both increasing and decreasing risk assessment behaviour depending on the initial defensive distance

should be borne in mind that there is an important adaptive balance between being too risk averse (BIS+) and too risk prone (BIS−). In other words, there is an optimal point of BIS activation: at high levels, the BIS is likely to resolve conflict in terms of FFFS-avoidance, which does not resolve the goal conflict in the longer term, although it may offer a temporary solution. In addition, a hyperactive BIS is likely to detect conflict at low level of objectively-defined conflict and thus engage in risk assessment cognitions/behaviours, which themselves generate more goal conflict (as perhaps seen in the pathological checking in OCD).

It is crucial to note here that anxiolytic drugs are not only specific to defensive approach as opposed to defensive avoidance but also affect defensive distance itself rather than specific defensive approach behaviours. If perceived intensity of threat is high (small defensive distance), an undrugged rat is likely to remain still. Under these conditions (lower grey arrow in Figure 2.1B), an anxiolytic drug will increase risk assessment (this will increase approach to the source of threat). But, if perceived threat is medium, an undrugged rat is likely to engage in risk assessment behaviour. Under these conditions (upper grey arrow in Figure 2.1B), an anxiolytic drug will decrease risk assessment (which again increases approach to the source of threat) and replace it with normal non-threat behaviours. Thus, the drug does not alter specific observable behaviours consistently but produces changes in behaviour that are consistent with an increase in the internal construct of defensive distance (Blanchard, Blanchard, Tom and Rodgers 1990; Blanchard and Blanchard 1990). This is a crucial point to understand about the new theory.

Conceptually, we see individual differences in defensive distance for a fixed real distance as a reflection of the personality dimension underlying punishment sensitivity (Corr and McNaughton, chapter 5). Anxiolytic drugs alter (internally perceived) defensive distance relative to actual external threat. If endogenous anxiolytic compounds can produce similar effects they would lead to trait differences in conflict sensitivity – they would alter trait anxiety. As will become clear below, trait anxiety, in this sense, would not be identical to neuroticism (which would control sensitivity to threat both with avoidance and approach). But we argue that neuroticism operates in the same general way, modifying defensive distance rather than having a consistent effect on any individual measurable behaviour.

Trait anxiety, in this sense, would represent a specific risk factor for generalized anxiety disorder that would be quite independent of risks for panic disorder, obsessive compulsive disorder or depression. (Anxiolytic drugs, as a class, do not affect these.) In this very narrow sense of trait anxiety, we can liken the low trait anxious individual to the drugged rat. We can thus use the X axis of Figure 2.1B (but not 2.1A) to indicate the types of defensive approach behaviour elicited by different perceived intensities of aversive stimuli produced by (a) changes in actual intensity; (b) trait differences in conflict sensitivity; (c) anxiolytic drug effects; and (d) their interactions. At present there is little clear evidence for such an anxiety-specific personality factor.

Similarly, the X axis of Figure 2.1A can be used to indicate the types of defensive avoidance behaviour elicited by different perceived

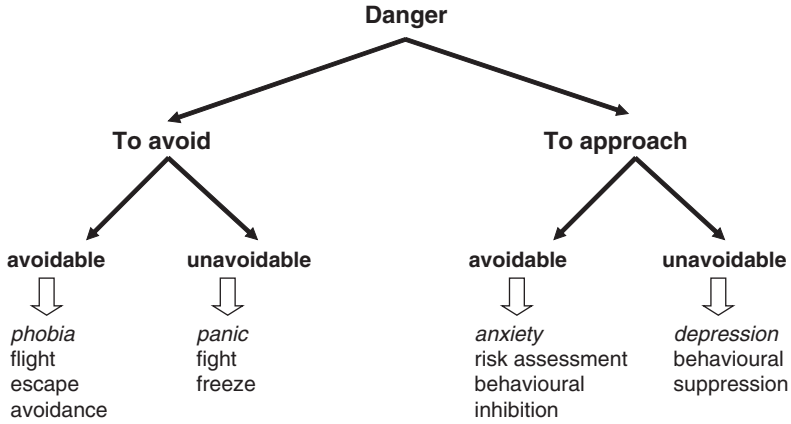

Figure 2.2 Categories of emotion and defensive response derived from defensive direction (avoid or approach the danger) and avoidability of the threat

intensities of aversive stimuli produced by (a) changes in the actual intensity of aversive stimuli; (b) trait differences in responses to aversive stimuli (different to trait differences in conflict sensitivity); (c) effects of drugs acting on threat sensitivity; and (d) their interactions. The bulk of the evidence for variation in proneness to DSM 'anxiety disorders', which include anxiolytic-insensitive symptomatologies such as panic and obsession, suggests that the key personality factor relates to a general punishment or threat sensitivity. We return to these issues in chapter 5.

So far, we have encompassed threats that should be avoided (defensive avoidance) but that produce different behaviours depending on whether the threat can be avoided or not (Figure 2.1A), as well as threats that should be approached but which in principle can be avoided. Indeed, the whole purpose of risk assessment behaviour (Figure 2.1B) is to allow approach to occur while avoiding the consequences of a perceived threat. There remains a further possibility (Figure 2.2). There can be threats that require approach (because of positive outcomes that could be obtained) but where the aversive consequence is perceived as unavoidable and where it is so great as to prevent the appetitive behaviour from occurring. This last possibility has not been subjected to the kind of analysis on which *The Neuropsychology of Anxiety* (1982) is based but has been tentatively identified with depression (McNaughton 1993).

Goals and goal conflict

A critical aspect of the recent formulations of the theory is that conflict is something that (from the point of view of the BIS) occurs between goals more than it does between stimuli or responses or action patterns. For those raised in a behaviourist environment it is natural to talk about conditioning of responses or the elicitation of innate responses. But behaviour is not simply controlled by some chain of stimulus-response connections (McNaughton 1989; Cahill, McGaugh and Weinberger 2001). Even well-conditioned behaviour is not invariant and what is important in determining the behaviour actually observed is the nature of the goal held in the animal's mind. Animals immediately produce completely novel response sequences to reach the unchanged goal location when their original response is blocked (Towe and Luschei 1981; Hinde 1966). Thus the conflict that activates the BIS is one between goals experienced by the subject rather than one inherent in a paradigm. In the case of human personality this realization has important implications: for example, it is not sufficient to manipulate reward and punishment without first assessing or manipulating expectations (Corr 2001).

Goal conflict, as a concept, has interesting implications. First, it should be clear that where there are equal tendencies to approach two incompatible goals the core problem to be resolved is independent of the motivational systems supporting the goals. This provides a simple account for the common effects of anxiolytic drugs on approach-approach, approach-avoidance, and avoidance-avoidance conflicts – while motivationally different, they have in common goal conflict. Second, it should be noted that goal conflict is only a significant problem when competing goals are approximately equally activated. In all other circumstances a simple winner-take-all mechanism will solve the problem. Thirdly, but less obviously, when the net worth of two goals is balanced we would expect evolution to favour risk aversion. Getting a larger reward is not advantageous in the long run if you are regularly running the risk of getting killed to obtain it rather than selecting a smaller, safe reward. Fourthly, and a corollary to the third point, conflict can best be resolved by gaining additional information to determine the true level of risk.

We have now entered the conceptual heart of the BIS: once conflict, in the sense of a close balance between competing goals, is detected, there is a selective potentiation of the power of affectively negative current perceptions and affectively negative remembered consequences. Affectively positive ones (although increased by simple drive summation) are not potentiated by conflict. In simple approach-avoidance, this will favour avoidance over approach. There are thus three distinct

elements to consider in relation to anxiety (but not fear): approach, avoidance, and the conflict between the two. It will be important for our analysis below that while fear and anxiety are fundamentally distinct, there will be many cases where anxiety (as indexed by anxiolytic action) involves an amplification of fear. There will also be cases where anxiety involves an amplification of frustration. Amplification of fear and of frustration occur through quite distinct neural circuits.

We see anxiety, then, as being most often generated by *concurrent* and equivalent activation of fear (or frustration) and approach systems, with the BIS acting to assess risk, and increase risk aversion in conflict situations. However, conflict is not restricted to approach-avoidance: approach-approach and avoidance-avoidance conflicts are also possible – and theoretically operate in the same way as approach-avoidance conflict.

Behavioural inhibition

A key aspect of conflict, from which the BIS derived its name, is that *prepotent* behaviour (both approach and avoidance) is inhibited. The result can be pure behavioural inhibition (behavioural quiescence) or exploratory and risk assessment behaviour or displacement activity. However, behavioural inhibition itself is so paradigmatic that it can appear more fundamental than the conflict that we have suggested gives rise to it.

Thus, in 'conditioned suppression', a stimulus classically conditioned with a shock suppresses responding despite there being no response-shock contingency. This is usually seen as a form of conditioned fear in which one might, therefore, 'not see any conflict, but only the impossibility of an escape response' (Frederico Graeff, personal communication). However, conditioned suppression appears to be insensitive to anxiolytic drugs unless the conditioning takes place in the same apparatus as the operant testing (i.e., it is 'on the baseline'). This, together with a range of other data (Gray and McNaughton 2000, Appendix 1 and Appendix 8), suggests that contextual conditioning is resulting in approach-avoidance conflict and, in particular, eliciting defensive quiescence that (unlike freezing proper) is sensitive to anxiolytic drugs (Melia, Ryabinin, Corodimas, Wilson and LeDoux 1996).

Behavioural elicitation

Although termed 'the behavioural inhibition system', the BIS is, and has always been, postulated to generate additional outputs related to exploration, attention and arousal. It is the *prepotent* conflicting

behaviours that are inhibited and, while they can be replaced by simple quiescence, they are more usually replaced by special behaviours designed to resolve the conflict (or occasionally by displacement activities).

The elicitation of behaviour by conflict is particularly obvious in the work of the Blanchards (see above). They showed that behavioural quiescence at high levels of threat was replaced, at intermediate levels of defensive approach, with rearing and a range of related anxiolytic-sensitive behaviours. Defensive burying is another particularly characteristic threat-elicited, anxiolytic-sensitive behaviour that has been extensively studied by Treit and colleagues (Degroot, Kashluba and Treit 2001; Gray, Terlecki, Treit and Pinel 1981; Menard and Treit 1996a, 1996b, 1999; Treit and Fundytus 1988; Treit, Robinson, Rotzinger and Pesold 1993). In the 'shock-probe burying test' rats are shocked by an electrified probe, and the duration of time that they spend spraying bedding material towards the probe (i.e., burying) is the major index of 'anxiety'. Standard anxiolytic drugs suppress this burying behaviour, and abolish the elevations in plasma corticosterone and adrenaline induced by the probe-shock. The suppression of burying by the benzodiazepines does not appear to be secondary to behavioural sedation, associative learning deficits or analgesia. Critically, 'defensive burying is an interesting behaviour not least because it involves approach to the source of noxious stimulation, and because it is so reliably and strongly elicited by a single aversive experience ... [and] unconditioned burying of novel objects in the absence of shock has also been observed' (Blampied and Kirk 1983). Thus, burying fulfils our major criterion for an anxiety-related reaction in that it involves *approach* to a source of potential threat. Of course, when no conflict is present, the animal would simply leave the situation (FFFS-controlled behaviour).

Psychological structure of the theory

It should be clear from the above that the most recent versions of the BIS theory, derived from animal data, are explicitly two-dimensional (Gray and McNaughton 2000; McNaughton and Corr 2004).

The first dimension, defensive direction, is categorical. It rests on a functional distinction between behaviours that remove an animal from a source of danger (FFFS-mediated) and those that allow it to approach a source of danger (BIS-mediated). These functions are ethologically and pharmacologically distinct and, on each of these separate grounds, can be identified with fear and anxiety, respectively. An important point is that the focus on approach and avoidance is derived from detailed experimental analysis of animal behaviour which subsumes, but does

not entirely match, the focus on certainty versus uncertainty of threat common to both clinical perspectives on fear and anxiety and the original ethological base of the current theory.

Shock-probe burying is probably the clearest, well-studied example of elicited behaviour that is sensitive to anxiolytics where the presence of the threat is absolutely certain and where the behaviour is elicited by approach to threat. In the conditioning literature, the most obvious example is in approach-avoidance conflict in the runway. Here, the rat is both certain of reward and equally certain of punishment. With low levels of shock the rat will suffer the shock to get the reward. At higher levels it will approach but not reach the goal and anxiolytic drugs increase this approach behaviour in both cases (changing defensive distance but not reward-related distance).

The second dimension, defensive distance, is graded. It rests on a functional hierarchy that determines appropriate behaviour in relation to defensive distance (i.e., perceived distance from threat – a cognitive dimension). This, second, hierarchical functional dimension applies equally to fear and anxiety but is instantiated separately in each (anxiolytic drugs change it in one case but not the other).

Neural systems of fear and anxiety

Although based on only two dimensions, this theory is comprehensive, combining previous theories of fear and anxiety within a single consistent rubric. In the process, it includes a large number of brain structures ranging from the prefrontal cortex, at the highest level, to the periaqueductal grey, at the lowest level, assigning to each structure (a) a specific place in the theory; (b) a specific fundamental class of function; and (c) a specific class of mental disorder. Thus, the most fundamental change to the old view of the BIS is that, in the new theory, it is *distributed* among a number of neural structures. At the state level, this detailed pigeon-holing shatters the unity that might be expected from the normal linkage of personality (and genetics) to individual neurotic disorders. But it will be seen that at the trait level we can 'put Humpty Dumpty back together again', delineating a small set of classes of disorder, via an analysis of modulatory systems. But the result is not identical to the unitary personality perspective taken by Gray originally (1976) and as recently as 1982. In this section we detail the neural architecture of these systems.

General architecture

The concepts of defensive direction and defensive distance provide a two-dimensional schema within which, in principle, all defensive

behaviours can be categorized. The theory translates this two-dimensional psychological schema into a matching two-dimensional neurological one. The categorical distinction *between* defensive approach and defensive avoidance is translated into two distinct parallel streams of neural structures. The dimension of defensive distance is translated into the levels of a hierarchy of structures *within* each of the parallel streams.

The neural mapping of defensive distance into the two hierarchies is rendered simple by two architectural features. First, smaller defensive distances map to more caudal, subcortical neural structures while larger defensive distances map to more rostral, cortical neural structures with intermediate structures arranged in caudo-rostral order in between (see Figure 2.3). The result is a two-dimensional variant of the hierarchical organization originally proposed by Deakin and Graeff (1991). Second, this mapping occurs in a symmetrical fashion, with matching structures located within each of the parallel streams – often being different subdivisions or nuclei of the same named area.

Despite this symmetry, it should be noted that, given the functional distinction between fear (avoid threat) and anxiety (approach threat), fear is more likely than anxiety to be engaged with more immediate threats while anxiety is more likely to be engaged under conditions of distant or anticipated threat – with the balance varying as the intensity of the threat varies. Figure 2.3 therefore represents the relative extent of the neural systems controlling fear and anxiety as varying systematically. At the lower levels, fear has a greater neural representation and at the higher levels anxiety has a greater neural representation.

Finally, for simplicity, we have represented the levels of the system as each being reciprocally connected to adjacent levels. But, in practice, the prefrontal cortex, for example, can influence the periaqueductal gray directly (Floyd, Price, Ferry, Keay and Bandler 2000; Shipley, Ennis, Rizvi and Behbehani 1991; An, Bandler, Öngür and Price 1998), maintaining the topographic organization of more indirect connections. There will be similar by-passing of levels between all parts of the system. However, this has no significant consequences for the arguments about personality to be presented later.

Anxiolytic drugs as markers for the BIS

We have already appealed (but without detailed justification) to the effects of anxiolytic drugs as a basis for identifying behaviours associated with the BIS, and hence anxiety, and as a basis for distinguishing anxiety from fear. A post hoc justification for doing this is simply that it was successful. Defensive behaviours do fall into functional classes. The

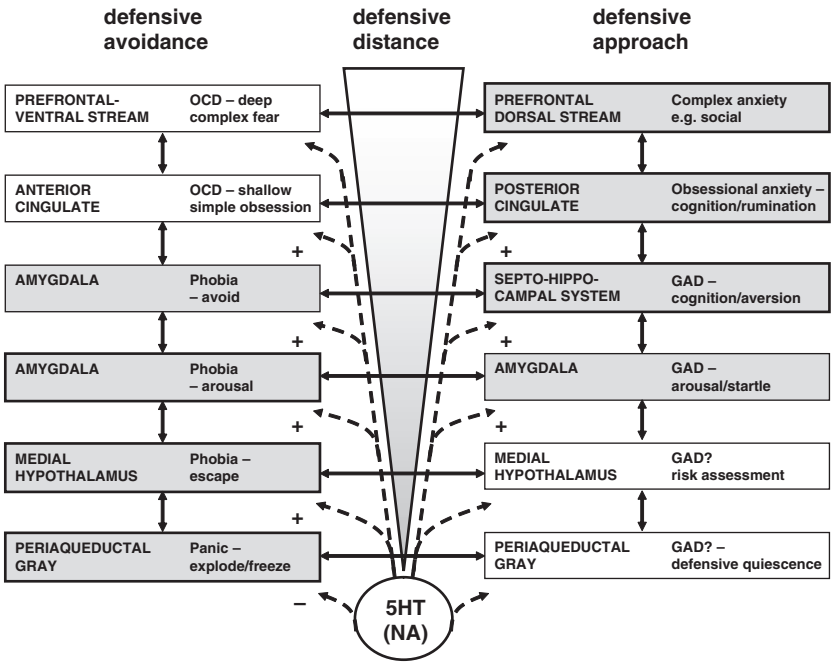

Figure 2.3 The two-dimensional defence system. On either side are defensive avoidance and defensive approach respectively (a categorical dimension). Each is divided, down the page, into a number of hierarchical levels. These are ordered from high to low (top to bottom) both with respect to neural level (and cytoarchitectonic complexity) and to functional level. Each level is associated with specific classes of behaviour and so symptom and syndrome. Syndromes are associated with hyper-reactivity of a structure and symptoms with high activity. Given the interconnections within the system (and effects of e.g., conditioning) symptoms will not be a good guide to syndromes

resultant classes are anxiolytic-insensitive and anxiolytic-sensitive respectively. But, equally important, is the fact that 'anxiolytic drugs' are effective in the clinic in treating disorders that clinicians recognize as having a common core, 'anxiety'.

This then permits an important strategic step. There is good agreement as to which drugs are anxiolytic and which not. Indeed this agreement obtains even when there is radical disagreement as to the definition of anxiety. This allows the use of the drugs as markers for a class of behaviours and it was the experimental analysis of the effects of the drugs (as a class) that gave rise to the concept of the BIS (Gray 1976, 1982). Modern developments in the pharmacology of the drugs now

also allow the identification of the critical brain systems mediating their actions – and so the neural location of the BIS.

The key point is that drugs must act on specific brain structures if they are to change specific emotions. They act like temporary lesions. Suitable alterations in those target structures should, then, produce sub-sets of the drugs' actions. Behavioural analysis of lesion effects can thus give us pointers as to where in the brain to look for functional changes underlying the drugs' actions. Once these are known, direct application of the drugs can determine the extent to which an area mediates systemic anxiolytic action. Prior to 1982, a problem with this approach was that all known anxiolytics acted via the neurotransmitter GABA and, in addition to anxiolytic action had various extents of euphoriant, addictive, muscle relaxant, anti-convulsant and other side-effects. With the advent of 'novel anxiolytics' that act through the serotonergic system we have drugs that have equivalent anxiolytic action (Wheatley 1982, 1990) but that have opposite side-effects. This allows us then to conclude that where any structure is affected, directly or indirectly, in the same manner by *both* classical and novel anxiolytic drugs, it is likely to be a key component of the BIS.

We will focus below on structures involved in the BIS and anxiety as it is in our treatment of these that the theory is most distinctive. The model we give below also deals with the FFFS and fear and our treatment of this is not covered in the same detail as it largely follows previous views (Deakin and Graeff 1991; Davis 1992b; LeDoux 1994; Graeff 1994; Gray and McNaughton 2000).

We will consider many neural structures, from the periaqueductal gray to the prefrontal cortex. For all of these structures it should be emphasized that we are dealing with only some parts of them. Particularly in the case of cingulate and frontal cortex, while we assign to parts of them specific defensive functions, this does not imply that any large part is devoted to defence as opposed to other affective systems. Nor do we imply that they are devoted to emotion as opposed to cognition. The amygdala is particularly noteworthy here. It can be viewed as more concerned with affect than cognition. But it is generally accepted to be important for all types of emotion not just fear and anxiety. Our allocation of both fear and anxiety to it is, then, consistent with its additional roles in various appetitive emotions.

Periaqueductal gray

The lowest neural level at which integrated defensive behaviour is controlled is the periaqueductal gray (PAG). As we will see, despite

being associated with the smallest defensive distances, it plays at least some role in anxiolytic action and so the BIS, although its contribution to the FFFS is much greater. Its role, here, is represented at the bottom left of Figure 2.3, associated with *undirected* escape/panic (Deakin and Graeff 1991).

The PAG contains functionally discrete areas (Holstege 1989; Zhang and Barrett 1990; Shipley, Ennis, Rizvi and Behbehani 1991; Carrive, Leung, Harris and Paxinos 1997; Bandler and Shipley 1994) that are topographically organized with respect to specific outputs to areas that control, e.g., autonomic responses (Carrive and Bandler 1991) and with respect to higher-level inputs from areas such as the amygdala (Rizvi, Ennis, Behbehani and Shipley 1991), prefrontal cortex (Shipley, Ennis, Rizvi and Behbehani 1991; Floyd, Price, Ferry, Keay and Bandler 2000; Reinvang, Magnussen, Greenlee and Larsson 1998; An, Bandler, Öngür and Price 1998; Bandler, Keay, Floyd and Price 2000) and particularly medial hypothalamus (Canteras, Simerly and Swanson 1994; Veening, Buma, Ter Horst, Roeling, Luiten and Nieuwenhuys 1991) – all of which are considered separately below.

Anxiolytics act directly on the ventral PAG to affect conditioned hypoalgesia (Harris and Westbrook 1995; Fanselow 1991), a passive coping response. Other anxiolytic-sensitive, passive coping behaviours are controlled by the ventral PAG (Bandler, Price and Keay 2000; Bandler and Shipley 1994) including contextual fear (Aboufatima, Chait, Dalal and De Beaurepaire 1999; Carrive, Leung, Harris and Paxinos 1997; Fanselow 1991) and suppression of bar-pressing in a conflict task (Liebman, Mayer and Liebeskind 1970). More active, anxiolytic-sensitive coping behaviours are controlled by the dorsal PAG (De Souza, Schenberg and Carobrez 1998; Matheus and Guimaraes 1997; Matheus, Nogueira, Carobrez, Graeff and Guimaraes 1994), including + maze open arm entries (Audi, de Oliveira and Graeff 1991), social interaction (Kask, Rägo and Harro 1998) and fear-potentiated startle (Woo, Pucak, Kye, Matus and Lewis 1997).

The PAG also, and more clearly, mediates anxiolytic-insensitive defensive behaviours. The lateral portion of the PAG controls the immediate activity burst in response to a shock but not conditioned freezing – and so is doubly dissociated from the ventral PAG (Fanselow 1991). It is also generally involved in confrontational defensive reactions (Bandler, Price and Keay 2000), including flight and rage (Bandler 1982), and it is strongly activated by the presence of a predator (Canteras and Goto 1999). These lateral, fear-related portions of the PAG receive input from the anterior cingulate cortex, which we will suggest below is a higher level of the fear control system.

The functional and anatomical topographic organization of PAG suggests it contains two distinct, intertwined defence systems – one anxiolytic-sensitive, one anxiolytic-insensitive – that we can relate to fear and anxiety (Fanselow 1991). It also appears to support distinct systems related to escapable and inescapable threat (Bandler and Shipley 1994; Bandler, Price and Keay 2000; Bandler, Keay, Floyd and Price 2000; Keay and Bandler 2002). It may then be topographically organized not only with respect to functions related to fear and anxiety but also depression (McNaughton 1993).

We suggest, below, that monoamine input exerts a general control of the entire defence system. But an unexpected feature of serotonergic modulation is that the lowest level (panic) is suppressed by input that activates higher levels. This explains not only the differential effects of many drugs but also such apparently anomalous phenomena as relaxation-induced panic (Graeff 1994).

Consistent with this neural differentiation, the strong genetic homogeneity of most neurotic disorders is only partially shared by panic. Neurotic disorder and panic share only about half of their genetic control, each having a distinct other half (Scherrer, True, Xian *et al.* 2000). In the case of panic, then, genetic influences on anxiety, via polymorphisms of aminergic systems, could operate in parallel with panic susceptibility, via polymorphisms of cholecystokinin (CCK) systems (Wang, Valdes, Noyes, Zoega and Crowe 1998a; Wang, Valdes, Noyes, Zoega and Crowe 1998b). This strengthens the picture, derived from epidemiology, of panic as a distinct entity that can be both a cause and a symptom of anxiety and can also occur alone.

Hypothalamus

Above the periaqueductal gray, in the medial hypothalamus, we have *directed* escape/phobic escape (Deakin and Graeff 1991). The hypothalamus is topographically connected to the PAG (Veening, Buma, Ter Horst, Roeling, Luiten and Nieuwenhuys 1991) as well as to higher levels of the defence hierarchy such as the prefrontal cortex (Floyd, Price, Ferry, Keay and Bandler 2001) that are themselves topographically connected to PAG.

Anxiolytics act directly on the dorsomedial hypothalamus (DMH) to reduce the aversive reaction produced by DMH stimulation (Milani and Graeff 1987) and GABA blockade of the DMH has 'anxiolytic' effects in the + maze, increasing open arm entries. The hypothalamus also contains the supramammillary area which is the direct site of action of anxiolytics for a range of effects mediated by changes in hippocampal

theta (see below) as well as being an area that controls defensive behaviour through its interactions with a range of areas including the PAG (Pan and McNaughton 2004). In particular, the supramammillary area controls a range of anxiolytic-sensitive behaviours including ambulation in the open field, contextual but not simple fear conditioning, consolidation of passive avoidance, punished responding in a conflict schedule, suppression in a fixed interval schedule and suppression in a differential reinforcement of low rates schedule (see Pan and McNaughton 2004, for review).

Amygdala

The amygdala controls active avoidance/phobic avoidance (Davis 1992b; LeDoux 1994). We have explicitly separated the components of the amygdala that deal with autonomic arousal and with active avoidance behaviour. Given the complexity of the amygdala (which includes areas with both cortical and subcortical architectonics) this is not unreasonable. However, our main reason for making this particular separation in our model, at its present stage of development, will be discussed in the next section. We also include the amygdala in both of the parallel hierarchies.

For many, the amygdala was a glaring omission from Gray's 1982 hippocampal theory of anxiety. However, at that time, this set of structures seemed involved in avoidance in general (mediated by what was, then, named the Fight-Flight System, FFS) rather than in the behavioural inhibition specifically affected by anxiolytic drugs. Even now, the parallels between anxiolytic action and hippocampal lesions are much closer (with respect to both effects and lacks of effect) than those between anxiolytic action and amygdala lesions (Gray and McNaughton 2000).

However, since 1982 it has become well accepted that the amygdala is involved in the control of both fear and anxiety (LeDoux 1994). In particular, anxiolytic drugs of all chemical classes act directly on the amygdala to reduce the arousal associated with anxiety (Davis 1992b), and this arousal is not mediated by the septo-hippocampal system (McNish, Gewirtz and Davis 1997). We are faced, then, with an amygdala that appears to mediate some but not all aspects of anxiolytic action, as well as a hippocampus that appears to mediate some but not all aspects of anxiolytic action. There is also significant overlap in the behaviours controlled by each – which is not surprising given their extensive interconnections (Gray and McNaughton 2000).

How can 'the amygdala' control both fear and anxiety? First we should note that it has equivalent involvement in many other types of motivation, positive and negative. It must be differentiated to deal with these and so fear and anxiety would be similarly separated. 'The amygdala' achieves these multiple separations at least, in part, because it is a complex set of highly differentiated cortical and subcortical structures. The boundaries of the amygdalar complex are not well defined and may include the 'extended amygdala' (Davis and Shi 1999). Conversely, the term 'amygdala', even without extension, is viewed by some as a set of distinct structures rather than being a unitary entity with multiple parts (Swanson and Petrovich 1998).

Whether fundamentally unitary or an arbitrary set of unrelated parts, it is clear that some parts of 'the amygdala' are functionally distinct from other parts in terms of mediating anxiolytic action. It appears that the anxiolytic-sensitive parts (with the highest density of benzodiazepine receptors) are the lateral and basal nuclei, with the central nucleus being insensitive (Davis 1992a).

Septo-hippocampal system

Above the amygdala, within the defensive approach system, we have the hippocampal formation. This constituted the core of Gray's 1982 neuropsychology of anxiety and is still the central structure in the currently proposed hierarchy. It also remains special within the theory in that it is at present the only complex area that is represented in only one of the two hierarchies.

To it we attribute cognitive aspects of conventional anxiety and generalized anxiety disorder (McNaughton 1997). However, as we noted above, the arousal associated with anxiety is controlled by the amygdala (Davis 1992b) not the septo-hippocampal system (McNish, Gewirtz and Davis 1997). So, within the defensive approach hierarchy we place a component of the amygdala below the septo-hippocampal system. By implication, therefore, there could be two forms of generalized anxiety disorder: one, more hippocampally centered, in which pathologically increased negative affective bias results in increased arousal; and a second, more amygdala centred, in which pathologically increased arousal results in increased negative cognitive bias. Both of these could, then, present clinically in a similar fashion.

An important point is that in both of these cases we have good evidence for direct effects of anxiolytic drugs producing distinct effects in these different neural targets (Gray and McNaughton 2000). Equally, active avoidance involves equivalent effects on cognition and arousal

that are not sensitive to anxiolytic drugs. This is the basis for the three different boxes labelled 'amygdala' in Figure 2.3. Further work is required to precisely identify the different neural components of the amygdala corresponding to each.

The origin and core of Gray's theory was the extensive similarities between the behavioural effects of anxiolytic drugs and hippocampal lesions. When the theory was expanded (Gray and McNaughton 2000; McNaughton and Corr 2004) this core had been hugely strengthened by the extension of this similarity to novel anxiolytic drugs. As noted above, these drugs do not interact with the $GABA_A$ receptor and so do not share the side-effects of classical anxiolytics. The parallels between anxiolytic action and hippocampal dysfunction cannot now be, as they could have been in 1982, attributed to the anti-convulsant action, for example, of the classical anxiolytics. The novel anxiolytics are, if anything, pro-convulsant.

More importantly, both classical and novel anxiolytics are effective in tests thought to be specific to hippocampal-sensitive forms of memory (McNaughton and Morris 1992; McNaughton and Morris 1987; Tan, Kirk, Abraham and McNaughton 1990; Tan, Kirk, Abraham and McNaughton 1989; Money, Kirk and McNaughton 1992). This links anxiolytic action to changes in memory function of the sort typically attributed to the hippocampus.

Equally important for the 1982 theory was the fact that anxiolytic drugs produce characteristic changes in hippocampal electrical activity. By 2000 this was shown to be true of all classes of anxiolytic drug, including those (like anti-depressants) that have no overlapping side-effects with classical anxiolytics (Coop and McNaughton 1991; Coop, McNaughton, Warnock and Laverty 1990; Coop, McNaughton and Scott 1992; McNaughton and Coop 1991; Zhu and McNaughton 1991a, 1991b, 1994a, 1994b, 1994c, 1995a), 1995b.

A further link with memory is forged by the fact that all these drugs have immediate neural effects that change little with time and have immediate actions in tests of animal learning – while the truly anxiolytic (as opposed to euphoriant and muscle relaxant) clinical actions of even the classical anxiolytics take time to develop (Wheatley 1990). The drugs appear, then, to reduce the formation of new threatening memories leaving old ones intact. This is a parallel to the more anterograde than retrograde character of hippocampal amnesia.

While massive and consistent across many domains of evidence, the above linking of anxiolytic drugs and the hippocampus was correlational. Many of the parallels could be attributed to the fact that anxiolytics alter noradrenergic input to the hippocampus (McNaughton

and Mason 1980) but some could not. Now, recent data have shown that intra-cranial anxiolytic injections that specifically reduce hippocampal theta frequency change both this and noradrenergic-insensitive behaviour as extensively as systemic injections (Woodnorth and McNaughton 2002). Importantly, when theta frequency is specifically changed by intra-cranial injections, formation of spatial memory is changed to an equivalent extent (Pan and McNaughton 1997). Thus 'hippocampal effects' of anxiolytic drugs can be attributed to these two distinct changes the drugs produce in the control of hippocampal theta as well as direct effects of the drugs on the hippocampus itself (Crestani, Lorez, Baer *et al.* 1999).

It is important to emphasize here that inclusion of any structure within the distributed network that is the BIS does not imply that its role in the BIS is that structure's sole raison d'etre. In our theory the hippocampus resolves conflicts that are largely cognitively laden (as in delayed matching to sample) as much as it does those that are emotionally laden (as in the innate suppression of a rat's 'pre-cat' behaviours in response to the smell of a cat). The theory in its present form assigns cognitive conflict resolution more to the entorhinal cortex and response-oriented conflict resolution more to the subiculum. However, it is likely that future elaboration of the theory will extend this parcellation to the hippocampus proper – there being evidence that the septal pole of the hippocampus is more involved in cognitive and the temporal in emotional control (Bannerman, Rawlins, McHugh *et al.* 2004).

Cingulate cortex

As with the amgydala, the cingulate cortex has distinct parts, each with different roles within the new theory. We consider each in turn.

Anterior cingulate Above the amygdala, in the stream of fear-related structures, we place the anterior cingulate cortex. It controls more complex active avoidance that will require a greater degree of anticipation and a less tight temporal linkage of warning stimuli with actual threat than the amygdala. Higher-level processing, here, does not imply less involvement in fundamental features of defence. Anterior cingulate is involved in the perception of pain (Koyama, Tanaka and Mikami 1998; Chang and Shyu 2001; Davis 2000; Coghill, Talbot, Evans *et al.* 1994; Davis, Wood, Crawley and Mikulis 1995), the production of anger (Dougherty, Shin, Alpert *et al.* 1999), Pavlovian fear conditioning (Knight, Smith, Stein and Helmstetter 1999) and avoidance learning (Kubota, Wolske, Poremba, Kang and Gabriel 1996).

Likewise, anterior cingulate lesions impair avoidance and lick suppression conditioned to an aversive stimulus (Bussey, Everitt and Robbins 1997).

Anterior cingulate thus deals with fundamental outputs of the FFFS – but involves stimulus inputs that may be as complex as guilt (Shin, Dougherty, Orr *et al.* 2000) with a focus on the affective rather than sensory aspects of pain (Rainville, Duncan, Price, Carrier and Bushnell 1997). In particular, we see the anterior cingulate as controlling active avoidance behaviours that include those that cannot be terminated by safety signals. There is a wide range of both innate and acquired rituals of this sort. Hand washing to avoid infection is an example. We, following others, thus assign their pathological form, obsessive compulsive disorder, to the anterior cingulate (Rapoport 1989; Ebert, Speck, Konig, Berger, Hennig and Hohagen 1997).

However, using the idea of defensive distance as the basis for speculation, we suggest that the anterior cingulate deals with relatively simple 'surface' expectations of nebulous threat (with prefrontal cortex dealing with deeper, more complex, expectations). Likewise, using the idea of defensive direction, we suggest that it deals only with obsessional active avoidance with posterior cingulate dealing with obsessional passive avoidance. Also, as with all of the other areas we include in Figure 2.3, the cingulate is held to deal with goal representations. More detailed motor control is elsewhere. In the case of the cingulate this control involves compulsions controlled largely by the basal ganglia (Rapoport 1989).

Our present allocation of anterior cingulate cortex to defensive avoidance is tentative. A possible role in defensive approach is suggested by involvement in the resolution of conflicts between approach and avoidance (MacDonald, Cohen, Stenger and Carter 2000; Riekkinen, Kuitunen and Riekkinen 1995) and in more general response conflicts 'in which a prepotent response tendency has to be overcome' (Barch, Braver, Akbudak, Conturo, Ollinger and Snyder 2001; Bussey, Muir, Everitt and Robbins 1996). Indeed, there is evidence that it is more involved in conflict monitoring than in selection for action (Botvinick, Nystrom, Fissell, Carter and Cohen 1999; Carter, Braver, Barch, Botvinick, Noll and Cohen 1998; Carter, Macdonald, Botvinick *et al.* 2000). These data would, nonetheless, be consistent with our assignment of anterior cingulate to the active defence system if the tasks used (e.g., Stroop test) are in fact eliciting *multiple responses* (Diehl, Dinner, Mohamed *et al.* 2000) that conflict in the attempt to achieve a *single goal*. The paradigm case here is mirror drawing. This involves a single clear goal but a high level of competition between prepotent and correct

response tendencies and is not dependent on the BIS (Gray and McNaughton 2000). The inhibitory aspects of anterior cingulate function in avoidance may also relate more to the correct timing of responses held in working memory (Gabriel 1990) and the co-ordination of response sequences (Kermadi, Liu and Rouiller 2000; Ochsner, Kosslyn, Cosgrove *et al.* 2001; Procyk and Josephy 2001) than to conflict per se.

There is also evidence that anterior cingulate is involved in the generation of mania (Blumberg, Stern, Martinez *et al.* 2000) and in Pavlovian reward conditioning (Parkinson, Willoughby, Robbins and Everitt 2000). This suggests 'that the anterior cingulate cortex may be involved in learning about the significance of stimuli that predict both aversive and appetitive events, thus endowing these stimuli with both negative and positive affective value' (Bussey, Everitt and Robbins 1997). So, given its anatomical complexity, it is possible that it contains components of each of the BAS, FFFS and BIS. Certainly, pain and Stroop tasks activate different parts of anterior cingulate cortex (Derbyshire, Vogt and Jones 1998; Peterson, Skudlarski, Gatenby, Zhang, Anderson and Gore 1999) and different parts appear to be involved in more cognitive and more emotional processing respectively (Whalen, Bush, McNally *et al.* 1998; Kwan, Crawley, Mikulis and Davis 2000; Takenouchi, Nishijo, Uwano, Tamura, Takigawa and Ono 1999). Defensive approach and defensive avoidance may then be represented in both anterior and posterior cingulate systems (Gabriel 1990) rather than, as we suggest here, distributed between them.

Posterior cingulate Posterior cingulate cortex is anatomically close to the hippocampal formation and like the hippocampus shows theta rhythm controlled from the medial septum (Feenstra and Holsheimer1979; Borst, Leung and MacFabe 1987) – making its function as likely to be altered by anxiolytic drugs as is that of the hippocampus. The parallels are strengthened by the fact that, unlike the anterior cingulate cortex but like anxiolytic drugs and hippocampus, posterior cingulate is involved in water maze learning (e.g., Riekkinen, Kuitunen and Riekkinen 1995) and high interference working memory tasks (Murray *et al.* 1989) and seems specifically involved in behavioural inhibition (Berger, Weikart, Bassett and Orr 1986).

Consistent with our linking of posterior cingulate to hippocampal function, it appears to deal with longer-term encoding of information as compared to anterior cingulate which appears to deal with shorter term encoding (Gabriel 1990) and to contribute to dysfunction in dementia (Minoshima, Foster and Kuhl 1994; Ishii, Sasaki, Yamaji, Sakamoto, Kitagaki and Mori 1997; Joyce, Rio, Ruttimann *et al.* 1994; Maddock,

Garrett and Buonocore 2002; Minoshima, Giordani, Berent, Frey, Foster and Kuhl 1997). It is noteworthy here that spatial dysfunction resulting from posterior cingulate damage, like hippocampal amnesia, is anterograde but not retrograde (Katayama, Takahashi, Ogawara and Hattori 1999).

As noted in relation to anterior cingulate, an important point about the fundamental division between defensive approach and defensive avoidance, for which we are arguing, is that there should be both fear-related and anxiety-related forms of obsession. Hand washing is a paradigmatic form of the former – a simple avoidance response removes the organism from danger and allows it to proceed about its normal affairs. We would argue that, 'fear of the dark', given our behavioural analysis above, is one candidate for an anxiety that lacks safety signals. It should be seen as anxiety rather than fear since it involves entering a threatening dark area from a safe lit area.

Fear of the dark can also be viewed as assigning threat to a set of locations and posterior cingulate cortex appears to be involved in spatial analysis particularly in the dark (Harkin and Whishaw 2002; Sutherland, Whishaw and Kolb 1988; Hirono, Mori, Ishii *et al.* 1998; Cooper, Manka and Mizumori 2001; Riekkinen, Kuitunen and Riekkinen 1995; Cooper and Mizumori 1999) although its exact involvement and the contribution of fibres of passage remains to be determined (Neave, Lloyd, Sahgal and Aggleton 1994; Meunier and Destrade 1997; Neave, Nagle, Sahgal and Aggleton 1996; Warburton, Aggleton and Muir 1998).

A related form of anxiety is agoraphobia (which in the theory would be better classified as 'agoranxiety'). This and other equivalent possible higher-order anxieties are classified by a lack of any simple avoidance strategy for the danger (which requires a high level of the defence system for their processing) and the fact that what is required for normal function is the capacity to approach and deal with the source of threat (which engages the defensive approach, anxiety, system in addition to the pure fear system). A possibility, then, is that pathology of the posterior cingulate cortex could give rise to pure agoraphobia. (This is not inconsistent with the suggestion that most presenting agoraphobia is the result of conditioning to pathological panic – primarily controlled by the periaqueductal grey.) Space, here, may simply be a special case of stimulus complexity or involvement of contextual factors since verbally mediated threat can also be processed by posterior cingulate (Maddock and Buonocore 1997).

At least in the case of agoraphobia, the clinical condition appears only weakly sensitive to anxiolytic drugs. This leads us to the possibility that,

having used the drugs to define anxiety in terms of approach to danger, the latter definition may take precedence. Posterior cingulate may be an area that we would want to see as part of the BIS even with behaviours that are not sensitive to anxiolytic drugs (the tool we have used so far in this section). In what could be argued are the most extreme cases of clinical anxiety, resistant to both psychological and pharmacological treatment, lesions of the cingulate have been used as treatment with some degree of success (Marks, Birley and Gelder 1966; Powell 1981; Rapoport 1989). However, it is not clear from the data on such cases as to whether it is fear or anxiety (in terms of the current theory) that is the critical problem.

Prefrontal cortex

Ventral stream At the top left hand side of Figure 2.3 we have the ventral stream of prefrontal cortex. This is, of course, a hierarchy of structures in itself not a single structure. It also includes (as we noted the cingulate might include) components of the BAS (Figure 2.4) with cells that are sensitive to the valence and value of reinforcement or related behaviours (O'Doherty, Kringelbach, Rolls, Hornak and Andrews 2001; Pratt and Mizumori 2001; Poucet 1997) including positive sensations (Francis, Rolls, Bowtell *et al.* 1999). But we have insufficient evidence at present to sub-divide it with respect to symptoms and syndromes. To it we assign those expectations of threat that involve the most complex assessment and the greatest distance in the future. Such assessments would involve processes as complex as gender stereotyping (Milne and Grafman 2001). This would suggest that there may be a form of 'deep' obsessive compulsive disorder that is to some extent neurally distinct from more 'surface' obsession – but still, nonetheless, involves simple avoidance of, rather than approach to, the source of danger. This suggestion is consistent with the fact that both cingulate and prefrontal damage can alleviate obsessionality (Powell 1981) and that abstract forms of punishment (e.g., monetary loss) appear to be represented in the ventral stream of frontal cortex (O'Doherty, Kringelbach, Rolls, Hornak and Andrews 2001). There are some indications that BIS output (possibly from the dorsal stream of the prefrontal cortex, see below) suppresses activity in the ventral stream (Simpson, Snyder, Gusnard and Raichle 2001; Simpson, Drevets, Snyder, Gusnard and Raichle 2001).

Dorsal stream Like cingulate lesions, prefrontal lesions have been used with some success to treat otherwise intractable anxiety (Powell 1981; Marks, Birley and Gelder 1966) and we would assign the

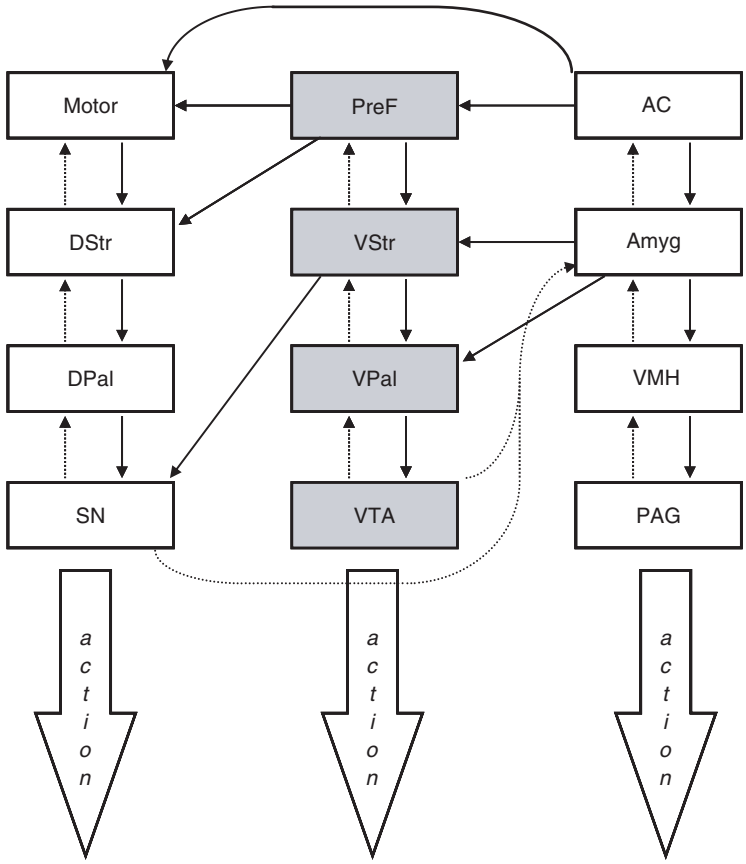

Figure 2.4 Structures included by Gray in the behavioural approach system (left two columns) with a suggested hierarchical organization similar to that of the defence systems. We argue in the text that the BAS is instantiated only within the column of shaded structures (operating on goal representations) rather than the unshaded ones (that operate on response rather than goal selection). Abbreviations: AC = anterior cingulate; Amyg = amygdala; DPal = dorsal pallium; DStr = dorsal striatum; PAG = periaqueductal gray; VMH = ventromedial hypothalamus; VPal = ventral pallium; VStr = ventral striatum; VTA = ventral tegmental area

highest levels of control of anxiety to the dorsal stream of frontal cortex. Like the hippocampus, the dorsal stream appears to be involved in dealing with interference (MacDonald, Cohen, Stenger and Carter 2000) and given the involvement of the hippocampus in contextual

tasks, it is noteworthy that cells in the dorsal (as opposed to the ventral) stream of prefrontal cortex are sensitive to the context of reinforcement (Watanabe, Hikosaka, Sakagami and Shirakawa 2002). The dorsal stream could, therefore, involve a variety of complex anxieties, in particular, social anxiety.[4]

Social behaviour is sufficiently complex that different aspects of it must be controlled at multiple levels of the defence system. Social situations also are likely to involve approach-avoidance conflict as they are at one and the same time a source of some of the most potent rewards and punishments faced by social organisms. Both imaging of those with social anxiety disorder compared to controls and imaging of changes induced by effective treatment indicate a fairly consistent pattern of changes in activation, which is most obvious in the dorsolateral prefrontal cortex (Argyropoulos, Bell and Nutt 2001; Furmark, Tillfors and Matteinsdottir 2002; Nutt, Bell and Malizia 1998; Van der Linden, Van Heerden and Warwick 2000). Similar results have been obtained with anxiety (and cortisol increases) induced by maternal separation both acutely in Rhesus monkeys (Rilling, Winslow, O'Brien, Gutman, Hoffman and Kilts 2001) and chronically in human infants. Given the complexity of prefrontal cortex there must be many other higher-level forms of anxiety to be described.

Behavioural approach system

We now have an outline of the FFFS and the matching components of the BIS. The revised BIS theory also has a central place for the *Behavioural Approach System* (BAS) – the BIS would often be activated with the simultaneous activation of the FFFS and the BAS (when there is approach-avoidance conflict). However, the BAS remains conceptually distinct from the FFFS and the BIS. All three systems can be viewed as hierarchically organized (Figure 2.4). Gray has previously (Gray and McNaughton 1996; Gray, Feldon, Rawlins, Hemsley and Smith 1991) described the BAS as having a 'caudate' component (left column in the figure) and an 'accumbens' component (shaded boxes in the figure). However, he also made clear that 'accumbens holds a list of subgoals making up a given motor program and is able to switch through the list in an appropriate order, but to retrieve the specific content of each step, it needs to call up the appropriate subroutine by way of its connections to the [caudate] system' (Gray and McNaughton 1996). Such caudate

[4] This suggestion and the literature we quote in the following paragraph were provided by Dr Caroline Bell.

motor command sub-routines are quite distinct from the affect-laden goals that are the subject of the FFFS, BAS and BIS (Gray and McNaughton 2000). We will, therefore, take here the BAS, proper, to be instantiated only in the structures represented in the figure by filled boxes.

As with the FFFS, the hierarchical organization of the BAS makes it difficult for any part of it to control overall BAS sensitivity. Where a personality factor is to alter such sensitivity generally, we must look for appropriate modulatory systems. The most likely neural candidate here is the mesolimbic system that employs the monoamine dopamine as its transmitter (mirroring the modulation by the monoamine serotonin of the FFFS and BIS). At the hormonal level, endogenous opioids are likely candidates.

The idea that the accumbens is a key node of the BAS is consistent with its involvement in appetitive arousal, facilitation of reward processes, and flexible response sequences including approach to safety signals (Ikemoto and Panksepp 1999).We cannot treat the dopamine system as homogenous, however. In the prefrontal cortex there is often a greater release of dopamine to aversive stimuli than is shown in the nucleus accumbens. It can also show increased dopamine release to both appetitive and aversive stimulation at times when the nucleus accumbens shows an increase to appetitive but a decrease to aversive stimuli (Di Chiara, Loddo and Tanda 1999). The BAS is further discussed by Pickering and Smillie in chapter 4.

From syndrome to sensitivity: putting Humpty Dumpty back together again

The key feature of our present view is that, independent of the precise correctness of the details suggested above, defensive distance and defensive direction map onto a series of distinct neural modules, to each of which can be attributed a particular class of function and so generation of a particular symptomatology, e.g., panic, phobia, obsession. These 'symptoms' may be generated in several different ways:

- as a normally adaptive reaction to their specific eliciting stimuli;
- at maladaptive intensity, as a result of excessive sensitivity to their specific eliciting stimuli;
- at maladaptive intensity, as a result of excessive activation of a related structure by its specific eliciting stimuli but where the 'symptoms' are not excessive given the level of input from the related structure.

For example, pathologically excessive anxiety could generate panic with the latter, in itself, being entirely appropriate to the level of apprehension experienced. Conversely pathological panic could, with repeated experience, condition anxiety with the level of the latter being appropriate to the panic experienced despite the anxiety being nominally pathological from the point of view of overall function.

This very modular view of the defence system, partitioned into distinct syndrome and symptom-specific components, was developed largely on the basis of animal experiments. But the linking of this view to terms such as panic, phobia and obsession is also justified by the clinical effects of drugs – taken class by class. As shown in Table 2.2, phobia, anxiety, panic, obsession and depression are dependent on distinct brain systems in that drugs that affect one need not affect another. For example, both benzodiazepines and buspirone are anxiolytic. But benzodiazepines (with a few exceptions such as alprazolam) do not affect depression and buspirone does not affect panic. Anxiety, depression and panic must each, then, depend on different parts of the brain. This separability of effects (comparing *classes* of drugs) is mapped by the theory to the distinct levels of the defence system. A multitude of specific behaviours, symptoms and syndromes can each, then, be pigeon-holed within a multitude of neural structures. While being a satisfactory explanation of the plethora of clinical phenomena this seems to shatter completely the idea, fundamental to the notion of a personality factor, that clusters and indeed swathes of such phenomena can have some fundamental unity, which is based on a personality.

Personality theory could be rescued, of course, by a simple appeal to the fact that genetically speaking, there seems to be a common fundamental predisposition to the plethora of clinical neurotic phenomena even though that predisposition manifests differently in different individuals (Kendler, Prescott, Myers and Neale 2003; Andrews, Stewart, Morris-Yates, Holt and Henderson 1990). However, it can be rescued much more directly. The same pharmacology (Table 2.2) that allows us, through a comparison of classes of drug, to differentiate syndromes allows us, when we look at individual drugs, to arrive at a similar perspective to the genetic one. The action of many clinically effective drugs is best viewed as an interaction with more global modulatory systems. For example, 5HT neurones innervate virtually the entire defence system (Figure 2.3). Drugs such as imipramine or specific serotonin re-uptake inhibitors that have a general effect on 5HT synapses, therefore, have more general clinical actions. They can affect anxiety, depression and panic because they increase the levels of 5HT in the different parts of the system controlling each. Even so, their

Table 2.2 *Pharmacological dissection of disorders. Various classes of drugs effective in treating neurotic disorders and their relative effects on different neurotic syndromes and the extent to which they share classical anxiolytic side-effects (muscle relaxant; anti-convulsant, sedative, addictive). Exceptional effects of individual members of a class are ignored (e.g., the anti-depressant and panicolytic actions of specific benzodiazepines such as alprazolam). It should be noted that anti-depressant monoamine oxidase inhibitors in particular phenelzine, are like novel anxiolytics (novel) such as buspirone and tricyclic drugs such as imipramine that have separate anxiolytic and anti-depressant action. They treat depression but also appear particularly effective in treating atypical depression (in which many symptoms overlap anxiety disorders but are resistant to anxiolytic drugs). They have not been reported to be effective in generalized anxiety. Key: class, classical anxiolytics such as benzodiazepines, barbiturates and meprobamate; CMI, Clomipramine; IMI, imipramine and closely related tricylic anti-depressants; MAOI, MonoAmine Oxidase Inhibitor; novel, novel, 5HT1A active, anxiolytics such as buspirone; SSRI, Specific Serotonin Reuptake Inhibitor; 0, no effect; – reduction; –, extensive reduction; +, increase; ( ), small or discrepant effects. From McNaughton (2002), Stein, Vythilingum and Seedat (2004)*

	class	novel	IMI	CMI	MAOI	SSRI
Simple phobia	0[a]	?	0	?	(–)	(–)
Generalized anxiety	–	–	–	–	0?	–
Social phobia	–	(–)	0	(–)	–	–
Panic attacks	0[b]	0	–	–[c]	–	–
Obsessions/Compusions	0	(–)	(–)	–	(–)	–
Unipolar depression	0	–	–	–	–	–
Atypical depression	0	?	(–)	?	–	?

Notes:
[a] Sartory, MacDonald and Gray (1990).
[b] Excluding alprazolam, e.g., Sanderson, Wetzler and Asnis (1994).
[c] Gentil *et al.* (1993).

effects on, say, anxiety are not linked to, say, their concurrent effects on depression. These are each the result of independent effects of 5HT in different areas of the brain and of differentiation between 5HT systems (Deakin 1999).

It should be noted here that the genetic influences on the 5HT system that have been identified so far in humans, and that could easily underlie personality factors, operate to alter the system generally rather than impacting on specific receptors. Indeed, via actions on enzymes

rather than receptors or uptake systems, genes could have even more widespread actions than tricyclic and related drugs.

So, comparison of drug classes can be used to dissect out different parts of the defence system. But this comparison must involve several different drugs within each class if specific conclusions are to be drawn about specific brain systems. Conversely, the systems as a joint whole, and each system individually, may be globally susceptible to modulation controlled by the biological substrates underlying personality. Humpty Dumpty in one sense remains broken but in another has been put back together again. In detail, then, the system underlying clinical drug action consists of two sets of parallel, interconnected modules dealing with defensive avoidance and defensive approach respectively. Superimposed on these specialized modules are general modulatory systems.

It would be expected, and seems on current evidence to be the case, that it is these latter modulatory systems that are crucial for personality. There is also a conceptual requirement for some such wholistic control. At least with the BIS, anxiolytics clearly alter defensive distance. They alter which point of the neural hierarchy is in control given progressive variations in the external situation – and they do so in a lawful manner. Assuming that the control of fear by the monoamines operates in a similar manner to the control of anxiety by anxiolytic drugs we would expect the personality factor of 'punishment sensitivity' would be one that simply alters the internal defensive distance in relation to any particular real distance. Put another way, a personality factor of fearfulness multiplies the level of fear experienced to a particular stimulus, producing many different levels with different stimuli. It does not consistently produce a particular class of fear-related behaviour – and it is only the latter that are linked to specific modules of the system outlined in Figure 2.3.

BAS, FFFS and BIS

With certain caveats, our argument has now come almost full circle. We start and finish with the idea that personality factors operate in a relatively simple fashion over large swathes of cognition, emotion and their related behavioural output.

Our caveats relate to the connection between factors and behavioural output and to the number and nature of the factors. There is a mass of defensive behaviour that can be pigeon-holed within a two dimensional matrix that is replicated at the functional/psychological and the neural levels. Global personality factors will interact with the different cells of

the matrix to produce somewhat different patterns of output depending on the specific sensitivities of those cells. In factor analytic terms this should lead to substantial shared variance across a wide range of variables but to no particular variable having a much higher loading than any other on the factor. In our current analysis we will need to consider factors relating to global threat sensitivity (acting directly on the FFFS and indirectly on the BIS), to more specific conflict sensitivity (acting on the BIS) and, of course, global reward sensitivity (acting directly on the BAS and indirectly on the BIS). We can, and will below, consider these three systems in their global form, ignoring the differences in pattern of response between individuals discussed already. Clinicians would also need to concern themselves with a specific panic-related factor (which supplements threat sensitivity as a source of genetic variance in panic) but this seems unlikely to be significant for the experiments normally carried out by personality researchers.

The left hand side of Figure 2.3 describes the neural machinery of the FFFS. It copes with an explicit danger that can be explicitly escaped or avoided. Obsession can be viewed as a special case where active avoidance is required but where it is in the nature of the danger (e.g., contagion) that there can be no explicit signal of safety. A single box in Figure 2.5 represents this entire system.

Figure 2.4 describes the neural machinery of the BAS and the right hand side of Figure 2.3 describes that of the BIS. Both are, like the FFFS, represented by a single box in Figure 2.5

The BIS is to some extent in parallel with the FFFS, but provides a range of functions when there is conflict. The most important of these functions with respect to the FFFS is that the BIS inhibits ongoing behaviour. Note, however, that the outputs of the BIS (Figure 2.5) include not only inhibition of avoidance (and approach) behaviour that would otherwise be produced but also increased arousal and attention.

Output from the BIS does not, however, entail immobility. An important active output, mediated by the septo-hippocampal system, is risk assessment behaviour, sometimes involving vigorous and extensive exploration. This behaviour can be seen as supporting the functions of the decision mechanism that would normally select approach or avoidance behaviour but which is incapable of doing so during conflict when (by definition) approach and avoidance are balanced. It gathers the information necessary to tip the balance in favour of approach (if the threat proves less than initially perceived) or avoidance (if the threat proves greater). While activation of the BIS inhibits avoidance behaviour (Figure 2.5), it does not decrease the motivational aspects of fear or frustration. Rather, the normal resolution of conflict by the BIS involves

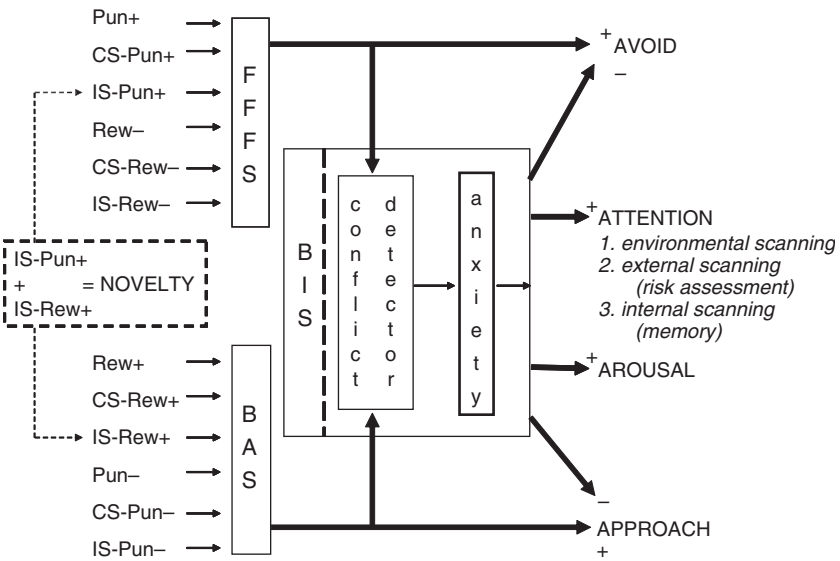

Figure 2.5 Relationship between stimuli, the Fight-Flight-Freeze System (FFFS), the Behavioural Approach System (BAS) and the Behavioural Inhibition System (BIS). Inputs consist of rewards (Rew) or punishers (Pun) that may be presented (+) or omitted when expected (−) and of innate stimuli (IS) or conditioned stimuli (CS) that predict these events. Note that the compound CS-Pun− can stand for either a CS that predicts Pun− or for the omission of a CS that predicts Pun+. The simplest means of activating the BIS is concurrent activation of the FFFS and the BAS, i.e., approach-avoidance conflict. However, approach-approach conflict and avoidance-avoidance conflict (as in two-way avoidance) will also activate the BIS

an increase in the effects of fear or frustration that favours avoidance over approach.

The decision to approach or to avoid is affected in a subtractive fashion by activation of the opposing motivational tendency. This subtraction operates both with respect to which decision (approach or avoid depending on whether the net sum is affectively positive or negative) and with respect to the vigour of goal-directed behaviour once the choice is made. Thus, even if a rat decides to run down a runway and collect the food at the end, prior experience of a mild shock will often reduce the speed with which it runs. It is important to note that the simple antagonism of reward value by associated punishment and of punishment by associated reward is symmetrical, is independent of

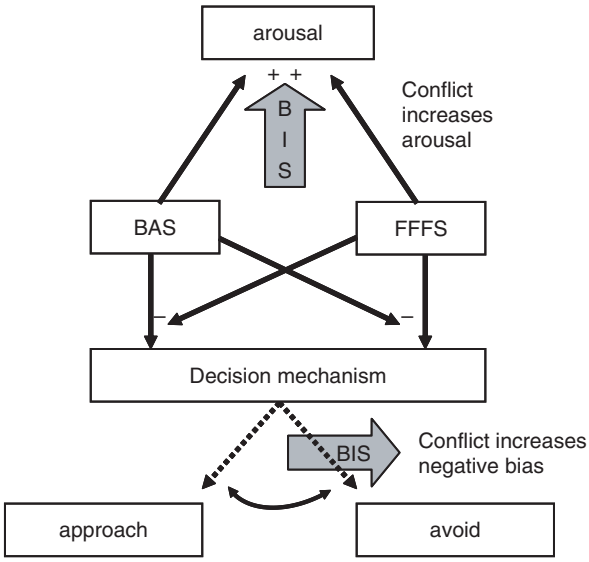

Figure 2.6 Effects of motivational systems on arousal and decision. The BAS and FFFS provide inputs that subtract to control decision and add to generate arousal. Arousal also operates on a much slower timescale than decision. The BIS increments arousal similarly to both the BAS and FFFS. It affects decision by increasing the effect of motivationally negative stimuli on decision

whether a response is required, and does not involve the BIS since it is not affected by anxiolytic drugs (McNaughton and Gray 1983).

In contrast to decision-making, the autonomic arousal accompanying approach or avoidance is affected in an additive fashion by activation of the opposing motivational tendency. This increased arousal also impacts on responses such as startle that are unrelated to the decision between the goals of the conflicting responses. Although 'fear potentiated startle' has received much analysis, it should be noted that 'hunger potentiated startle' also occurs (Drobes, Miller, Hillman, Bradley, Cuthbert and Lang 2001). The opposite interactions of the FFFS and BAS in decision-making and on arousal are shown in Figure 2.6 These different classes of computation must clearly be carried out by different parts of the brain.

Activation of the BIS by conflict (i.e., when approach and avoidance tendencies are not only each present but relatively closely matched in intensity of activation) also necessarily has different effects on choice

than it does on arousal. As far as the decision mechanism that selects approach or avoidance is concerned, detection of conflict by the BIS has three distinct effects: it suppresses approach and avoidance;[5] it increases the tendency to avoid (lower BIS arrow in Figure 2.6); and it elicits risk analysis behaviour. By contrast, the arousal mechanism that summates the intensity of approach and avoidance motivation has its activity potentiated rather than suppressed by conflict via the 'increase arousal' output of the BIS (upper BIS arrow in Figure 2.6). Increased arousal might result (when approach and avoidance are closely balanced and both are inhibited) in the release of extraneous 'displacement' activities.

We need, therefore, to add to the picture of the amygdala painted in the 2000 theory. It is generally accepted that the amygdala not only receives information about both positive and negative events but also controls 'emotional' output for both positive and negative events. It is known, at least for negative events, to be the site at which an incoming signal of threat (e.g., a simple stimulus relayed from the thalamus) is registered and then generates a cascade including both motor and autonomic output. Intensity of amygdala activation can be equated here with arousal. The amygdala would be the logical site to locate the summing of the arousal inputs (see Figure 2.6).

It is not clear whether anxiolytic drugs affect this summing, in its most fundamental form. Nor, to our knowledge, has their effect on positive, e.g., hunger-potentiated, startle been tested. It may be that both positive and negative arousal feed into the amygdala and are anxiolytic-sensitive. However, it is also possible that positive and negative arousal are individually anxiolytic-insensitive but that the amygdala also contains additional circuitry that can detect when there is an even balance between arousal due to approach tendencies and arousal due to avoidance tendencies. When it detects such a balance, it implements the 'increase arousal' output of the BIS. Certainly, whether the circuitry is simple or complex, it is not contained in the septo-hippocampal system (lesion of which does not affect, for example, fear potentiated startle). Equally certainly, circuitry involved in this control of arousal is located in the amygdala since this is where the anxiolytics act directly to alter arousal.

The critical point not emphasized in the 2000 theory is that the effect of conflict is asymmetric (negative bias – increasing avoidance only) for the decision-making mechanism but symmetric (affecting components

[5] The suppression of conflicting behaviours is quite specific. Not only does conflict encourage risk analysis behaviour it also (mentioned only in passing in the 2000 theory) can unmask other 'displacement' behaviours. This can only occur if the behavioural inhibition is specific to the conflicting behaviours.

of both approach and avoidance) for arousal. This entails differential neural control. It should also be noted that the time course for decision-making will be very swift, of the order of tens of milliseconds, while that for arousal is necessarily slow with autonomic and hormonal actions having latencies of the order of seconds. The mutually antagonistic interactions between the FFFS and BAS, independent of the BIS, are also not emphasized in the 2000 theory. This antagonism can be presumed to occur at all relative levels of activation of the two systems. By contrast it is only when their activations are fairly evenly balanced that conflict results and the BIS is activated to resolve the problem faced by the decision mechanism.

Conclusion

Our theory makes a categorical distinction between two systems: one controlling defensive avoidance (fear) and one controlling defensive approach (anxiety). Why should one attempt to give precise behavioural/psychopharmacological definitions of fear and anxiety when these are used interchangeably by the general public and in clinical psychiatry? The fast answer, of course, is that we can. But, more importantly, there are many confusions for members of the public and psychiatrists that our distinction lays to rest. Why do 'anxiolytic drugs' only affect some defensive responses and not others? It is not tautological for us to reply that it is only anxious defence (i.e., approach to threat) that these drugs affect. How can relaxation induce panic – a sign of fear? Because fear and anxiety are not only distinct but anxiety (as defined by us) often inhibits fear (as defined by us). Further, as noted by Graeff, the nature of the responses elicited by the two states are often opposite in kind (fear producing speed and anxiety slowness) although the autonomic reactions are similar. So, not only can we distinguish fear and anxiety, especially in the clinic, we must do so if we are to have a clear picture of the world – and some chance of ultimately being able to categorize genuine syndromes of defensive reactions.

Our theory (Figure 2.3) also invokes a second dimension of hierarchical organization that is both functional (in terms of defensive distance) and neural (in terms of rostro-caudal level and cytoarchitectonic complexity). This does not have quite the fundamental impact of our first dimension. But again, both for the public and the psychiatrist, it can make clear both the potential diversity of reactions and hence syndromes and also a means of categorizing a multitude in terms of a simple, externally defined dimension. Importantly, it explains why many different drugs are needed to cope with individual pathologies of defence.

These two dimensions account for the differentiation between different defensive behaviours and between different syndromes and symptoms. Serotonergic and noradrenergic fibres that essentially mediate global threat sensitivity modulate all the structures controlling defence. The different levels of each system and the two systems as a whole are heavily interconnected to allow parallel control by both 'quick and dirty' and 'slow and sophisticated' systems (LeDoux 1994) and to allow rapid switching between defensive approach and defensive avoidance as conditions change. The monoamine systems can be thought of as operating on longer timescales, underpinning therapeutic drug actions and providing the basis for personality variables that determine risk of morbidity. Critically, they can be thought of as interacting with all levels of the systems, acting on defensive distance (which selects the neural level for current control) – and so having a more unitary function than the various parts we have delineated.

Omitted from the above account is the nature of the interactions between the levels of the system. That these will not be entirely simple is shown by the example of relaxation-induced panic – the result of an inhibitory interaction between the outputs of the anxiety and fear systems (Graeff 1994). Also absent is the highly detailed topographic mapping between the levels (Risold and Swanson 1996; Bandler, Keay, Floyd and Price 2000; Heidbreder and Groenewegen 2003). Each component of the model of Figure 2.3, then, is not a simple box but a patchwork of modules; each arrow represents a mass of parallel connections. But these do not really complicate the theory. They represent strands that allow the choice of particular responses once both defensive direction and defensive distance have determined the general nature of the required response. Finally, we should note that the detailed account presented here is only of the control of acute reactions. Control can pass from one system to another in an instant. The reactions to chronic threats are different and controlled by distinct systems (Deakin 1999) as may be entities such as anti-social personality disorder (Deakin 2003). We turn to the specifics of the theory for personality in the next chapter.

References

Aboufatima, R., Chait, A., Dalal, A. and De Beaurepaire, R. (1999), Calcitonin microinjection into the periaqueductal gray impairs contextual fear conditioning in the rat, *Neuroscience Letters*, 275, 101–104

An, X., Bandler, R., Öngür, D. and Price, J.L. (1998), Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys, *Journal of Comparative Neurology*, 401, 455–479

Andrews, G., Stewart, G., Morris-Yates, A., Holt, P. and Henderson, S. (1990), Evidence for a general neurotic syndrome, *British Journal of Psychiatry*, 157, 6–12

Argyropoulos, S.V., Bell, C.J. and Nutt, D. (2001), Brain function in social anxiety disorder, *Psychiatric Clinics of North America*, 24, 707–722

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 (Berl)*, 105, 553–557

Bandler, R. (1982), Induction of 'rage' following microinjections of glutamate into midbrain but not hypothalamus of cats, *Neuroscience Letters*, 30, 183–188

Bandler, R., Keay, K.A., Floyd, N. and Price, J. (2000), Central circuits mediating patterned autonomic activity during active vs. passive emotional coping, *Brain Research Bulletin*, 53, 95–104

Bandler, R., Price, J.L. and Keay, K.A. (2000), Brain mediation of active and passive emotional coping, *Progress in Brain Research*, 122, 331–347

Bandler, R. and Shipley, M.T. (1994), Columnar organization in the midbrain periaqueductal gray: modules for emotional expression?, *Trends in Neuroscience*, 17, 379–389

Bannerman, D.B., Rawlins, J.N.P, McHugh, S.B., Deacon, R.M.J, Yee, B.K., Bast, T., Zhang, W.-N., Pothuizen, H.H.J and Feldon, J. (2004), Regional dissociation within the hippocampus: memory and anxiety, *Neuroscience and Biobehavioral Reviews*, 28, 273–283

Barch, D.M., Braver, T.S., Akbudak, E., Conturo, T., Ollinger, J. and Snyder, A. (2001), Anterior cingulate cortex and response conflict: effects of response modality and processing domain, *Cerebral Cortex*, 11, 837–848

Berger, T.W., Weikart, C.L., Bassett, J.L. and Orr, W.B. (1986), Lesions of the retrosplenial cortex produce deficits in reversal learning of the rabbit nictitating membrane response: implications for potential interactions between hippocampal and cerebellar brain systems, *Behavioral Neuroscience*, 100, 802–809

Blampied, N. and Kirk, R.C. (1983), Defensive burying: effects of diazepam and oxprenolol measured in extinction, *Life Sciences*, 33, 695–699

Blanchard, D.C. and Blanchard, R.J. (1988), Ethoexperimental approaches to the biology of emotion, *Annual Review of Psychology*, 39, 43–68

(1990), Effects of ethanol, benzodiazepines and serotonin compounds on ethopharmacological models of anxiety in N. McNaughton and G. Andrews (eds), *Anxiety* (Dunedin: Otago University Press), pp. 188–199

Blanchard, D.C., Blanchard, R.J., Tom, P. and Rodgers, R.J. (1990), Diazepam changes risk assessment in an anxiety/defense test battery, *Psychopharmacology (Berl)*, 101, 511–518

Blanchard, R.J. and Blanchard, D.C. (1989), Antipredator defensive behaviors in a visible burrow system, *Journal of Comparative Psychology*, 103(1), 70–82

(1990a), An ethoexperimental analysis of defense, fear and anxiety in N. McNaughton and G. Andrews (eds), *Anxiety* (Dunedin: Otago University Press), pp. 124–133

(1990b), Anti-predator defense as models of animal fear and anxiety in P.F. Brain, S. Parmigiani, R.J. Blanchard and D. Mainardi (eds), *Fear and Defence* (Church Harwood Academic Publishers), pp. 89–108

Blanchard, R.J., Griebel, G., Henrie, J.A. and Blanchard, D.C. (1997), Differentiation of anxiolytic and panicolytic drugs by effects on rat and mouse defense test batteries, *Neuroscience and Biobehavioral Reviews*, 21, 783–789

Blumberg, H.P., Stern, E., Martinez, D., Ricketts, S., De Asis, J., White, T., Epstein, J., McBride, P.A., Eidelberg, D., Kocsis, J.H. and Silbersweig, D.A. (2000), Increased anterior cingulate and caudate activity in bipolar mania, *Biological Psychiatry*, 48, 1045–1052

Borst, J.G.G, Leung, L.-W. S. and MacFabe, D.F. (1987), Electrical activity of the cingulate cortex. II, Cholinergic modulation, *Brain Research*, 407, 81–93

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S. and Cohen, J.D. (1999), Conflict monitoring versus selection-for-action in anterior cingulate cortex, *Nature*, 402, 179–181

Bussey, T.J., Everitt, B.J. and Robbins, T.W. (1997), Dissociable effects of cingulate and medial frontal cortex lesions on stimulus-reward learning using a novel Pavlovian autoshaping procedure for the rat: implications for the neurobiology of emotion, *Behavioral Neuroscience*, 111, 908–919

Bussey, T.J., Muir, J.L., Everitt, B.J. and Robbins, T.W. (1996), Dissociable effects of anterior and posterior cingulate cortex lesions on the acquisition of a conditional visual discrimination: facilitation of early learning vs. impairment of late learning, *Behavioural Brain Research*, 82, 45–56

Cahill, L., McGaugh, J.L. and Weinberger, N.M. (2001), The neurobiology of learning and memory: some reminders to remember, *Trends in Neurosciences*, 24, 578–581

Canteras, N.S. and Goto, M. (1999), Fos-like immunoreactivity in the periaqueductal gray of rats exposed to a natural predator, *Neuroreport*, 10, 413–418

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, *Journal of Comparative Neurology*, 348, 41–79

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, 206–215

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, 165–177

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D. and Cohen, J.D. (1998), Anterior cingulate cortex, error detection, and the online monitoring of performance, *Science*, 280, 747–749

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D. and Cohen, J.D. (2000), Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex, *Proceedings of*

the National Academy of Sciences of the United States of America, 97, 1944–1948

Chang, C. and Shyu, B.C. (2001), A fMRI study of brain activations during non-noxious and noxious electrical stimulation of the sciatic nerve of rats, *Brain Research*, 897, 71–81

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C. and Duncan, G.H. (1994), Distributed processing of pain and vibration by the human brain, *Journal of Neuroscience*, 14, 4095–4108

Coop, C.F. and McNaughton, N. (1991), Buspirone affects hippocampal rhythmical slow activity through serotonin$_{1A}$ rather than dopamine D_2 receptors, *Neuroscience*, 40, 169–174

Coop, C.F., McNaughton, N. and Scott, D.J. (1992), Pindolol antagonizes the effects on hippocampal rhythmical slow activity of clonidine, baclofen and 8-OH-DPAT, but not chlordiazepoxide and sodium amylobarbitone, *Neuroscience*, 46, 83–90

Coop, C.F., McNaughton, N., Warnock, K. and Laverty, R. (1990), Effects of ethanol and Ro 15–4513 in an electrophysiological model of anxiolytic action, *Neuroscience*, 35, 669–674

Cooper, B.G., Manka, T.F. and Mizumori, S.J.Y (2001), Finding your way in the dark: the retrosplenial cortex contributes to spatial memory and navigation without visual cues, *Behavioral Neuroscience*, 115, 1012–1028

Cooper, B.G. and Mizumori, S.J.Y (1999), Retrosplenial cortex inactivation selectively impairs navigation in darkness, *Neuroreport*, 10, 625–630

Corr, P.J. (2001), Testing problems in J.A. Gray's personality theory: a commentary on Matthews and Gilliland (1999), *Personality and Individual Differences*, 30, 333–352

Crestani, F., Lorez, M., Baer, K., Essrich, C., Benke, D., Laurent, J.P., Belzung, C., Fritschy, J.-M., Lüscher, B. and Mohler, H. (1999), Decreased $GABA_A$-receptor clustering results in enhanced anxiety and a bias for threat cues, *Nature Neuroscience*, 2, 833–839

Davis, K.D. (2000), The neural circuitry of pain as explored with functional MRI, *Neurological Research*, 22, 313–317

Davis, K.D., Wood, M.L., Crawley, A.P. and Mikulis, D.J. (1995), fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation, *Neuroreport*, 7, 321–325

Davis, M. (1992a), The role of the amygdala in conditioned fear in J.P. Aggleton (ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Function* (Wiley-Liss Inc.), pp. 255–305

(1992b), The role of the amygdala in fear and anxiety, *Annual Review of Neuroscience*, 15, 353–375

Davis, M. and Shi, C.J. (1999), The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety?, *Annals of the New York Academy of Sciences*, 877, 281–291

De Souza, M.M., Schenberg, L.C. and Carobrez, A.D.P (1998), NMDA-coupled periaqueductal gray glycine receptors modulate anxioselective

drug effects on plus-maze performance, *Behavioural Brain Research*, 90, 157–165

Deakin, J.F.W. (1999), Making sense of serotonin (5HT) and its role in common psychopathology in M. Tansella and G. Thornicroft (eds), *Common Mental Disorders in Primary Care: Essays in Honour of Professor Sir David Goldberg* (London and New York: Routledge), pp. 17–33

(2003), Depression and antisocial personality disorder: two contrasting disorders of 5HT function, *Journal of Neural Transmission*, 64, 79–93

Deakin, J.F.W and Graeff, F.G. (1991), 5-HT and mechanisms of defence, *Journal of Psychopharmacology*, 5, 305–315

Degroot, A., Kashluba, S. and Treit, D. (2001), Septal GABAergic and hippocampal cholinergic systems modulate anxiety in the plus-maze and shock-probe tests, *Pharmacology, Biochemistry and Behavior*, 69, 391–399

Derbyshire, S.W.G, Vogt, B.A. and Jones, A.K.P (1998), Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex, *Experimental Brain Research*, 118, 52–60

Di Chiara, G., Loddo, P. and Tanda, G. (1999), Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression, *Biological Psychiatry*, 46, 1624–1633

Diehl, B., Dinner, D.S., Mohamed, A., Najm, I., Klem, G., LaPresto, E., Bingaman, W. and Lüders, H.O. (2000), Evidence of cingulate motor representation in humans, *Neurology*, 55, 725–728

Dougherty, D.D., Shin, L.M., Alpert, N.M., Pitman, R.K., Orr, S.P., Lasko, M., Macklin, M.L., Fischman, A.J. and Rauch, S.L. (1999), Anger in healthy men: a PET study using script-driven imagery, *Biological Psychiatry*, 46, 466–472

Drobes, D.J., Miller, E.J., Hillman, C.H., Bradley, M.M., Cuthbert, B.N. and Lang, P.J. (2001), Food deprivation and emotional reactions to food cues: implications for eating disorders, *Biological Psychology*, 57, 153–177

Ebert, D., Speck, O., Konig, A., Berger, M., Hennig, J. and Hohagen, F. (1997), ^{1}H-magnetic resonance spectroscopy in obsessive-compulsive disorder: evidence for neuronal loss in the cingulate gyrus and the right striatum, *Psychiatry Research: Neuroimaging Section*, 74, 173–176

Eysenck, H.J. (1944), Type of personality: a factorial study of 700 neurotics, *Journal of Mental Sciences*, 90, 851–861

(1947), *Dimensions of Personality* (London: K. Paul Trench Trubner)

Fanselow, M. S. (1991), The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety in A. Depaulis and R. Bandler (eds), *The Midbrain Periaqueductal Gray Matter*. (New York: Plenum Press), pp. 151–173

Feenstra, B.W.A and Holsheimer, J. (1979), Dipole-like neuronal sources of theta rhythm in dorsal hippocampus, dentate gyrus and cingulate cortex of the urethane-anesthetized rat, *Electroencephalography and Clinical Neurophysiology*, 47, 532–538

Floyd, N.S., Price, J.L., Ferry, A.T., Keay, K.A. and Bandler, R. (2000), Orbitomedial prefrontal cortical projections to distinct longitudinal

columns of the periaqueductal gray in the rat, *Journal of Comparative Neurology*, 422, 556–578
(2001), Orbitomedial prefrontal cortical projections to hypothalamus in the rat, *Journal of Comparative Neurology*, 432, 307–328
Francis, S., Rolls, E.T., Bowtell, R., McGlone, F., O'Doherty, J., Browning, A., Clare, S. and Smith, E. (1999), The representation of pleasant touch in the brain and its relationship with taste and olfactory areas, *Neuroreport*, 10, 453–459
Furmark, T., Tillfors, M. and Matteinsdottir, I. (2002), Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive behaviour therapy, *Archives of General Psychiatry*, 59, 425–433
Gabriel, M. (1990), Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits, *Progress in Brain Research*, 85, 467–483
Gentil, V., Lotufo-Neto, F., Andrade, L., Cordás, T., Bernik, M., Ramos, R., Maciel, L., Miyakawa, E. and Gorenstein, C. (1993), Clomipramine, a better reference drug for panic/agoraphobia, I. Effectiveness comparison with imipramine, *Journal of Psychopharmacology*, 7, 316–324
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
Gray, D.S., Terlecki, L.J., Treit, D. and Pinel, J.P.J (1981), Effect of septal lesions on conditioned defensive burying, *Physiology and Behavior*, 27, 1051–1056
Gray, J.A. (1964), *Pavlov's Typology* (Oxford: Pergamon)
(1967), Disappointment and drugs in the rat, *Advancement of Science*, 23, 595–605
(1970), The Psychophysiological basis of introversion – extroversion, *Behaviour Research and Therapy*, 8, 249–266
(1975), *Elements of a Two-Process Theory of Learning* (London: Academic Press)
(1976), The behavioural inhibition system: a possible substrate for anxiety in M.P. Feldman and A.M. Broadhurst (eds), *Theoretical and experimental bases of behaviour modification* (London: Wiley), pp. 3–41
(1977), Drug effects on fear and frustration: possible limbic site of action of minor tranquilizers in L.L. Iversen, S.D. Iversen and S.H. Snyder (eds), *Handbook of Psychopharmacology*, vol. 8, *Drugs, Neurotransmitters and Behaviour* (New York: Plenum Press), pp. 433–529
(1982), *The Neuropsychology of Anxiety: an Enquiry into the Functions of the Septo-hippocampal System* (Oxford: Oxford University Press)
(1987), *The Psychology of Fear and Stress* (London: Cambridge University Press)
Gray, J.A., Feldon, J., Rawlins, J.N.P, Hemsley, D.R. and Smith, A.D. (1991), The Neuropsychology of Schizophrenia, *Behavioral and Brain Sciences*, 14, 1–20
Gray, J. A. and McNaughton, N. (1996), The neuropsychology of anxiety: reprise in D.A. Hope (ed.), *Perspectives on Anxiety, Panic and Fear* (Nebraska: University of Nebraska Press), pp. 61–134
(2000), *The Neuropsychology of Anxiety: an Enquiry into the Functions of the Septo-hippocampal System* (Oxford: Oxford University Press)

Harkin, A. and Whishaw, I.Q. (2002), Impaired spatial performance in rats with retrosplenial lesions: importance of the spatial problem and the rat strain in identifying lesion effects in a swimming pool, *Journal of Neuroscience*, 22, 1155–1164

Harris, J.A. and 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

Heidbreder, C.A. and Groenewegen, H.J. (2003), The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics, *Neuroscience and Biobehavioral Reviews*, 27, 555–579

Hinde, R.A. (1966), *Animal Behaviour* (New York: McGraw-Hill Book Company)

Hirono, N., Mori, E., Ishii, K., Ikejiri, Y., Imamura, T., Shimomura, T., Hashimoto, M., Yamashita, H. and Sasaki, M. (1998), Hypofunction in the posterior cingulate gyrus correlates with disorientation for time and place in Alzheimer's disease, *Journal of Neurology, Neurosurgery, and Psychiatry*, 64, 552–554

Holstege, G. (1989), Anatomical study of the final common pathway for vocalization in the cat, *Journal of Comparative Neurology*, 284, 242–252

Ikemoto, S. and Panksepp, J. (1999), The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking, *Brain Research Reviews*, 31, 6–41

Ishii, K., Sasaki, M., Yamaji, S., Sakamoto, S., Kitagaki, H. and Mori, E. (1997), Demonstration of decreased posterior cingulate perfusion in mild Alzheimer's disease by means of $H_2{}^{15}$ O positron emission tomography, *European Journal of Nuclear Medicine*, 24, 670–673

Joyce, E.M., Rio, D.E., Ruttimann, U.E., Rohrbaugh, J.W., Martin, P.R., Rawlings, R.R. and Eckardt, M.J. (1994), Decreased cingulate and precuneate glucose utilization in alcoholic Korsakoff's syndrome, *Psychiatry Research*, 54, 225–239

Kask, A., Rägo, L. and Harro, J. (1998), NPY Y_1 receptors in the dorsal periaqueductal gray matter regulate anxiety in the social interaction test, *Neuroreport*, 9, 2713–2716

Katayama, K., Takahashi, N., Ogawara, K. and Hattori, T. (1999), Pure topographical disorientation due to right posterior cingulate lesion, *Cortex*, 35, 279–282

Keay, K.A. and Bandler, R. (2002), Parallel circuits mediating distinct emotional coping reactions to different types of stress, *Neuroscience and Biobehavioral Reviews*, 25, 669–678

Kendler, K.S., Prescott, C.A., Myers, J. and Neale, M.C. (2003), The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women, *Archives of General Psychiatry*, 60, 929–937

Kermadi, I., Liu, Y. and Rouiller, E.M. (2000), Do bimanual motor actions involve the dorsal premotor (PMd), cingulate (CMA) and posterior parietal

(PPC) cortices? Comparison with primary and supplementary motor cortical areas, *Somatosensory and Motor Research*, 17, 255–271

Kimble, G.A. (1961), *Hilgard and Marquis' Conditioning and Learning* (New York: Appleton-Century-Crofts)

Knight, D.C., Smith, C.N., Stein, E.A. and Helmstetter, F.J. (1999), Functional MRI of human Pavlovian fear conditioning: patterns of activation as a function of learning, *Neuroreport*, 10, 3665–3670

Koyama, T., Tanaka, Y.Z. and Mikami, A. (1998), Nociceptive neurons in the macaque anterior cingulate activate during anticipation of pain, *Neuroreport*, 9, 2663–2667

Kubota, Y., Wolske, M., Poremba, A., Kang, E. and Gabriel, M. (1996), Stimulus-related and movement-related single-unit activity in rabbit cingulate cortex and limbic thalamus during performance of discriminative avoidance behavior, *Brain Research*, 721, 22–38

Kwan, C.L., Crawley, A.P., Mikulis, D.J. and Davis, K.D. (2000), An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli, *Pain*, 85, 359–374

LeDoux, J.E. (1994), Emotion, memory and the brain, *Scientific American*, 270, 50–59

Liebman, J.M., Mayer, D.J. and Liebeskind, J.C. (1970), Mesencephalic central gray lesions and fear-motivated behavior in rats, *Brain Research*, 23, 353–370

MacDonald, A.W. III, Cohen, J.D., Stenger, V.A. and Carter, C.S. (2000), Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control, *Science*, 288, 1835–1838

Maddock, R.J. and Buonocore, M.H. (1997), Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study, *Psychiatry Research: Neuroimaging Section*, 75, 1–14

Maddock, R.J., Garrett, A.S. and Buonocore, M.H. (2002), Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval, *Neuroscience*, 104, 667–676

Marks, I.M., Birley, J.L.T and Gelder, M.G. (1966), Modified leucotomy in severe agoraphobia: a controlled serial inquiry, *British Journal of Psychiatry*, 112, 757–769

Matheus, M.G. and Guimaraes, F.S. (1997), Antagonism of non-NMDA receptors in the dorsal periaqueductal grey induces anxiolytic effect in the elevated plus maze, *Psychopharmacology (Berl)*, 132, 14–18

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

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

(1993), Stress and behavioural inhibition in S.C. Stanford and P. Salmon (eds), *Stress: an Integrated Approach* (Academic Press), pp. 191–206

(1997), Cognitive dysfunction resulting from hippocampal hyperactivity: a possible cause of anxiety disorder, *Pharmacology, Biochemistry and Behavior*, 56, 603–611

(2001), Approach-avoidance conflict in W.E. Craighead and C.B. Nemeroff (eds), *The Corsini Encyclopedia of Psychology and Behavioral Science* (New York: John Wiley and Sons), pp. 126–127

(2002), Aminergic transmitter systems in H. D'haenen, J.A. Den Boer, H. Westenberg and P. Willner (eds), *Textbook of Biological Psychiatry* (John Wiley and Sons), pp. 895–914

McNaughton, N. and Coop, C.F. (1991), Neurochemically dissimilar anxiolytic drugs have common effects on hippocampal rhythmic slow activity, *Neuropharmacology*, 30, 855–863

McNaughton, N. and Corr, P.J. (2004), A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance, *Neuroscience and Biobehavioral Reviews*, 28, 285–305

McNaughton, N. and Gray, J.A. (1983), Pavlovian counterconditioning is unchanged by chlordiazepoxide or by septal lesions, *Quarterly Journal of Experimental Psychology*, 35B, 221–233

McNaughton, N. and Mason, S.T. (1980), The neuropsychology and neuropharmacology of the dorsal ascending noradrenergic bundle: a review, *Progress in Neurobiology*, 14, 157–219

McNaughton, N. and Morris, R.G.M (1987), Chlordiazepoxide, an anxiolytic benzodiazepine, impairs place navigation in rats, *Behavioural Brain Research*, 24, 39–46

(1992), Buspirone produces a dose-related impairment in spatial navigation, *Pharmacology, Biochemistry and Behavior*, 43, 167–171

McNish, K.A., Gewirtz, J.C. and Davis, M. (1997), Evidence of contextual fear after lesions of the hippocampus: a disruption of freezing but not fear-potentiated startle, *Journal of Neuroscience*, 17, 9353–9360

Melia, K.R., Ryabinin, A.E., Corodimas, K.P., Wilson, M.C. and LeDoux, J.E. (1996), Hippocampal-dependent learning and experience-dependent activation of the hippocampus are preferentially disrupted by ethanol, *Neuroscience*, 74, 313–322

Menard, J. and Treit, D. (1996a), Does tolerance develop to the anxiolytic effects of septal lesions, *Physiology and Behavior*, 59, 311–318

(1996b), Lateral and medial septal lesions reduce anxiety in the plus-maze and probe-burying tests, *Physiology and Behavior*, 60, 845–853

(1999), Effects of centrally administered anxiolytic compounds in animal models of anxiety, *Neuroscience and Biobehavioral Reviews*, 23, 591–613

Meunier, M. and Destrade, C. (1997), Effects of radiofrequency versus neurotoxic cingulate lesions on spatial reversal learning in mice, *Hippocampus*, 7, 355–360

Milani, H. and Graeff, F.G. (1987), GABA-Benzodiazepine modulation of aversion in the medial hypothalamus of the rat, *Pharmacology, Biochemistry and Behavior*, 28, 21–27

Miller, N.E. (1944), Experimental studies of conflict in J.M. Hunt (ed.), *Personality and the Behavioural Disorders* (New York: Ronald)

Milne, E. and Grafman, J. (2001), Ventromedial prefrontal cortex lesions in humans eliminate implicit gender stereotyping, *Journal of Neuroscience*, 21, NIL1–NIL6

Minoshima, S., Foster, N.L. and Kuhl, D.E. (1994), Posterior cingulate cortex in Alzheimer's disease, *Lancet*, 344, 895–895

Minoshima, S., Giordani, B., Berent, S., Frey, K.A., Foster, N.L. and Kuhl, D.E. (1997), Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease, *Annals of Neurology*, 42, 85–94

Money, E.A., Kirk, R.C. and McNaughton, N. (1992), Alzheimer's dementia produces a loss of discrimination but no increase in rate of memory decay in delayed matching to sample, *Neuropsychologia*, 30, 133–145

Murray, E.A., Davidson, M., Gaffan, D., Olton, D.S. and Suomi, S. (1989). Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. *Experimental Brain Research* 74, 173–186.

Neave, N., Lloyd, S., Sahgal, A. and Aggleton, J.P. (1994), Lack of effect of lesions in the anterior cingulate cortex and retrosplenial cortex on certain tests of spatial memory in the rat, *Behavioural Brain Research*, 65, 89–101

(1996), The effects of discrete cingulum bundle lesions in the rat on the acquisition and performance of two tests of spatial working memory, *Behavioural Brain Research*, 80, 75–85

Nutt, D., Bell, C.J. and Malizia, A.L. (1998), Brain mechanisms of social anxiety disorder, *Journal of Clinical Psychiatry*, 59, 4–9

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J. and Andrews, C. (2001), Abstract reward and punishment representations in the human orbitofrontal cortex, *Nature Neuroscience*, 4, 95–102

Ochsner, K.N., Kosslyn, S.M., Cosgrove, G.R., Cassem, E.H., Price, B.H., Nierenberg, A.A. and Rauch, S.L. (2001), Deficits in visual cognition and attention following bilateral anterior cingulotomy, *Neuropsychologia*, 39, 219–230

Okaichi, Y. and Okaichi, H. (1994), Effects of fimbria-fornix lesions on avoidance tasks with temporal elements in rats, *Physiology and Behavior*, 56, 759–765

Pan, W.-X. and McNaughton, N. (1997), The medial supramammillary nucleus, spatial learning and the frequency of hippocampal theta activity, *Brain Research*, 764, 101–108

(2004), The supramammillary area: its organization, functions and relationship to the hippocampus, *Progress in Neurobiology*, 74, 127–166

Parkinson, J.A., Willoughby, P.J., Robbins, T.W. and Everitt, B.J. (2000), Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: further evidence for limbic cortical-ventral striatopallidal systems, *Behavioral Neuroscience*, 114, 42–63

Peterson, B.S., Skudlarski, P., Gatenby, J.C., Zhang, H.P., Anderson, A.W. and Gore, J.C. (1999), An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems, *Biological Psychiatry*, 45, 1237–1258

Poucet, B. (1997), Searching for spatial unit firing in the prelimbic area of the rat medial prefrontal cortex, *Behavioural Brain Research*, 84, 151–159

Powell, G.E. (1981), A survey of the effects of brain lesions upon personality in H.J. Eysenck (ed.), *A Model for Personality* (Springer-Verlag), pp. 65–87

Pratt, W.E. and Mizumori, S.J.Y (2001), Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task, *Behavioural Brain Research*, 123, 165–183

Procyk, E. and Josephy, J.P. (2001), Characterization of serial order encoding in the monkey anterior cingulate sulcus, *European Journal of Neuroscience*, 14, 1041–1046

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B. and Bushnell, M.C. (1997), Pain affect encoded in human anterior cingulate but not somatosensory cortex, *Science*, 277, 968–971

Rapoport, J.L. (1989), The biology of obsessions and compulsions, *Scientific American*, 63–69

Reinvang, I., Magnussen, S., Greenlee, M.W. and Larsson, P.G. (1998), Electrophysiological localization of brain regions involved in perceptual memory, *Experimental Brain Research*, 123, 481–484

Riekkinen, P. Jr., Kuitunen, J. and Riekkinen, M. (1995), Effects of scopolamine infusions into the anterior and posterior cingulate on passive avoidance and water maze navigation, *Brain Research*, 685, 46–54

Rilling, J.K., Winslow, J.T., O'Brien, D., Gutman, D.A., Hoffman, J.M. and Kilts, C.D. (2001), Neural correlates of maternal separation in Rhesus monkeys, *Biological Psychiatry*, 49, 146–157

Risold, P.Y. and Swanson, L.W. (1996), Structural evidence for functional domains in the rat hippocampus, *Science*, 272, 1484–1486

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, *Journal of Comparative Neurology*, 303, 121–131

Sanderson, W.C., Wetzler, S. and Asnis, G.M. (1994), Alprazolam blockade of CO_2-provoked panic in patients with panic disorder, *American Journal of Psychiatry*, 151, 1220–1222

Sartory, G., MacDonald, R. and Gray, J.A. (1990), Effects of diazepam on approach, self-reported fear and psychophysiological responses in snake phobics, *Behaviour Research and Therapy*, 28, 273–282

Scherrer, J.F., True, W.R., Xian, H., Lyons, M.J., Eisen, S.A., Goldberg, J., Lin, N. and Tsuang, M.T. (2000), Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic, *Journal of Affective Disorders*, 57, 25–35

Shin, L.M., Dougherty, D.D., Orr, S.P., Pitman, R.K., Lasko, M., Macklin, M. L., Alpert, N.M., Fischman, A.J. and Rauch, S.L. (2000), Activation of anterior paralimbic structures during guilt-related script-driven imagery, *Biological Psychiatry*, 48, 43–50

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 A. Depaulis and R. Bandler (eds), *The Midbrain Periaqueductal Gray Matter* (New York: Plenum Press), pp. 417–448

Simpson, J.R. Jr., Drevets, W.C., Snyder, A.Z., Gusnard, D.A. and Raichle, M.E.(2001), Emotion-induced changes in human medial prefrontal cortex, II. During anticipatory anxiety, *Proceedings of the National Academy of Sciences of the United States of America*, 98, 688–693

Simpson, J.R. Jr., Snyder, A.Z., Gusnard, D.A. and Raichle, M.E. (2001), Emotion-induced changes in human medial prefrontal cortex, I. During cognitive task performance, *Proceedings of the National Academy of Sciences of the United States of America*, 98, 683–687

Stein, D.J., Vythilingum, B. and Seedat, S. (2004) Pharmacotherapy of phobias: a review, ch. 3, in Maj., M., Akiskal, H.S., López-Ibor, J.J., Okasha, A. (eds), *Evidence and Experience in Psychiatry,* vol. 7 *Phobias*

Sutherland, R.J., Whishaw, I.Q. and Kolb, B. (1988), Contributions of cingulate cortex to two forms of spatial learning and memory, *Journal of Neuroscience*, 8(6), 1863–1872

Swanson, L.W. and Petrovich, G.D. (1998), What is the amygdala?, *Trends in Neurosciences*, 21, 323–331

Takenouchi, K., Nishijo, H., Uwano, T., Tamura, R., Takigawa, M. and Ono, T. (1999), Emotional and behavioral correlates of the anterior cingulate cortex during associative learning in rats, *Neuroscience*, 93, 1271–1287

Tan, S., Kirk, R.C., Abraham, W.C. and McNaughton, N. (1989), Effects of the NMDA antagonists, CPP and MK-801 on delayed conditional discrimination, *Psychopharmacology*, 98, 556–560

(1990), Chlordiazepoxide reduces discriminability but not rate of forgetting in delayed conditional discrimination, *Psychopharmacology*, 101, 550–554

Towe, A.L. and Luschei, E.S. (1981), Preface in A.L. Towe and E.S. Luschei (eds), *Motor Coordination* (New York: Plenum Press), pp. vii–viii

Treit, D. and Fundytus, M. (1988), A comparison of buspirone and chlordiazepoxide in the shock-probe/burying test for anxiolytics, *Pharmacology, Biochemistry and Behavior*, 30, 1071–1075

Treit, D., Robinson, A., Rotzinger, S. and Pesold, C. (1993), Anxiolytic effects of serotonergic interventions in the shock-probe burying test and the elevated plus mase, *Behavioural Brain Research*, 54, 23–34

Van der Linden, G., Van Heerden, B. and Warwick, J. (2000), Functional brain imaging and pharmacotherapy in social phobia: single photon emission computed tomography before and after treatment with the selective serotoninreuptake inhibitor citalopram, *Progress in Neuropsychopharmacology and Biological Psychiatry*, 24, 419–438

Veening, J., Buma, P., Ter Horst, G.J., Roeling, T.A.P., Luiten, P.G.M. and Nieuwenhuys, R. (1991), Hypothalamic projections to the PAG in the rat: Topographical, immuno-electronmicroscopical and function aspects in A. Depaulis and R. Bandler (eds), *The Midbrain Periaqueductal Gray Matter* (New York: Plenum Press), pp. 387–415

Wang, Z., Valdes, J., Noyes, R., Zoega, T. and Crowe, R.R. (1998a), Possible association of a cholecystokinin promotor polymorphism (CCK_{-36CT}) with panic disorder, *American Journal of Medical Genetics*, 81, 228–234

(1998b), Possible association of a cholecystokinin promotor polymorphism (CCK_{-36CT}) with panic disorder, *American Journal of Medical Genetics*, 81, 228–234

Warburton, E.C., Aggleton, J.P. and Muir, J.L. (1998), Comparing the effects of selective cingulate cortex lesions and cingulum bundle lesions on water maze performance by rats, *European Journal of Neuroscience*, 10, 622–634

Watanabe, M., Hikosaka, K., Sakagami, M. and Shirakawa, S. (2002), Coding and monitoring of motivational context in the primate prefrontal cortex, *Journal of Neuroscience*, 22, 2391–2400

Whalen, P.J., Bush, G., McNally, R.J., Wilhelm, S., McInerney, S.C., Jenike, M.A. and Rauch, S.L. (1998), The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division, *Biological Psychiatry*, 44, 1219–1228

Wheatley, D. (1982), Buspirone: multicenter efficacy study, *Journal of Clinical Psychiatry*, 43(12), 92–94

(1990), The new alternatives in D. Wheatley (ed.), *In the Anxiolytic Jungle: Where Next?* (Chichester: John Wiley), pp. 163–184

Woo, T.U., Pucak, M.L., Kye, C.H., Matus, C.V. and Lewis, D.A. (1997), Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex, *Neuroscience*, 80, 1149–1158

Woodnorth, M.-A. and McNaughton, N. (2002), Similar effects of medial supramammillary or systemic injections of chlordiazepoxide on both theta frequency and fixed-interval responding, *Cognitive, Affective, and Behavioral Neuroscience*, 2, 76–83

Zhang, L. and Barrett, J.E. (1990), Interactions of corticotropin-releasing factor with antidepressant and anxiolytic drugs: Behavioural studies with pigeons, *Biological Psychiatry*, 27(9), 953–967

Zhu, X.-O. and McNaughton, N. (1991a), Effects of long-term administration of anxiolytics on reticular-elicited hippocampal rhythmical slow activity, *Neuropharmacology*, 30, 1095–1099

(1991b), Effects of long-term administration of imipramine on reticular-elicited hippocampal rhythmical slow activity, *Psychopharmacology*, 105, 433–438

(1994a), A comparison of the acute effects of a tricyclic and a MAOI antidepressant on septal driving of hippocampal rhythmical slow activity, *Psychopharmacology (Berl)*, 114, 337–344

(1994b), Effects of long-term administration of antidepressants on septal driving of hippocampal RSA, *International Journal of Neuroscience*, 79, 91–98

(1994c), The interaction of serotonin depletion with anxiolytics and antidepressants on reticular-elicited hippocampal RSA, *Neuropharmacology*, 33, 1597–1605

(1995a), Minimal changes with long-term administration of anxiolytics on septal driving of hippocampal rhythmical slow activity, *Psychopharmacology (Berl)*, 118, 93–100

(1995b), Effects of long-term administration of phenelzine on reticular-elicited hippocampal rhythmical slow activity, *Neuroscience Research*, 21, 311–316

(1995c), Similar effects of buspirone and chlordiazepoxide on a fixed interval schedule with long-term, low-dose administration, *Journal of Psychopharmacology*, 9, 326–330