Review

A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance

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Abstract

We present in this paper a picture of the neural systems controlling defense that updates and simplifies Gray’s “Neuropsychology of Anxiety”. It is based on two behavioural dimensions: ‘defensive distance’ as defined by the Blanchards and ‘defensive direction’. Defensive direction is a categorical dimension with avoidance of threat corresponding to fear and approach to threat corresponding to anxiety. These two psychological dimensions are mapped to underlying neural dimensions. Defensive distance is mapped to neural level, with the shortest defensive distances involving the lowest neural level (periaqueductal grey) and the largest defensive distances the highest neural level (prefrontal cortex). Defensive direction is mapped to separate parallel streams that run across these levels. A significant departure from prior models is the proposal that both fear and anxiety are represented at all levels. The theory is presented in a simplified form that does not incorporate the interactions that must occur between non-adjacent levels of the system. It also requires expansion to include the dimension of escapability of threat. Our current development and these proposed future extensions do not change the core concepts originally proposed by Gray and, we argue, demonstrate their enduring value.

Keywords: Two-dimensional neuropsychology; Symptomatology; Anxiety

Contents

1. The Behavioural Inhibition System, 2000 versus 1982 .............................................. 286
2. Anxiolytic drugs as markers for systems involved in anxiety ......................................... 288
2.1. The septo-hippocampal system. ........................................................................ 288
2.2. The amygdala ..................................................................... 288
2.3. The hypothalamus and periaqueductal gray .................................................. 289
2.4. Overview of the neural structures involved in fear and anxiety ............................... 289
3. Constructs for a theory of fear and anxiety .......................................................... 289
3.1. Reward and punishment. ........................................................................ 289
3.2. Fear and Anxiety—defensive direction ..................................................... 290
3.3. Defensive distance. ........................................................................ 290
3.4. Goal conflict . .......................................................................... 292
4. The two-dimensional defense system .......................................................... 292
4.1. Defensive avoidance ........................................................................ 292
4.2. Defensive approach ........................................................................ 294
4.3. An overview . ........................................................................ 296
5. The behavioural approach system ........................................................................ 297
6. The BAS, FFFS and BIS ................................................................... 297
7. Experimental tests of the theory ........................................................................ 299
8. Overview ............................................................................... 300
References ................................................................................ 300
This paper proposes a simple architecture for defensive systems based on only two dimensions. The first dimension is categorical. It rests on a functional distinction between behaviours that remove an animal from a source of danger and those that allow it to approach a source of danger. This two functions are executed by two parallel neural systems, one controlling fear and one anxiety, respectively. The second dimension is graded. It rests on a functional hierarchy that determines appropriate behaviour in relation to defensive distance (i.e. perceived distance from threat). This hierarchy of function applies equally to fear and anxiety and in each case is mapped to the neural level that controls behaviour. Smaller defensive distances map to more rostral, subcortical, neural structures while larger ones map to more rostral, cortical, neural structures. 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 to the periaqueductal grey, assigning a specific place in the theory, a specific fundamental class of function and a specific class of mental disorder to each.

Our classification covers essentially all of the conventionally recognised defense related disorders (phobias and anxieties). But, as emphasised by a referee of this paper, post-traumatic stress disorder is notably absent from this classification. Our reason for this is that, of all the disorders in the DSM classification, post-traumatic stress disorder is unique in being diagnosed in terms of its cause not its symptomatology. Post-traumatic stress disorder can include all of the symptoms of all the other disorders but not its symptomatology. Post-traumatic stress disorder can only change its fundamental nature. But they have sufficient basis for neurotic-introversion [98]. These systems then alter the sensitivity of the entire defense system with individual symptomatology within post-traumatic stress disorder reflecting extensive comorbidity—each element fitting into our standard classification.

The specific changes made in 2000 to the 1982 theory do not change its fundamental nature. But they have sufficient impact that the 2000 version should be read carefully as predictions cannot be based on prior knowledge of the 1982 version. The critical changed features are:

1. The Behavioural Inhibition System, 2000 versus 1982

The theory of the present paper involves relatively simple additions and adjustments that increase the symmetry of the theory of Gray and McNaughton (2000). The latter has not been dealt with in depth in the present paper. But, since it departs significantly from the better-known theory of Gray (1982), we summarise the critical differences below.

The most important differences of the 2000 theory compared to the 1982 theory are that: (1) it provides a clear distinction between fear and anxiety; (2) it provides a single means of defining the inputs to the BIS; and (3) it provides a specific account of the role of the hippocampus in human amnesia.

The specific changes made in 2000 to the 1982 theory do not change its fundamental nature. But they have sufficient impact that the 2000 version should be read carefully as predictions cannot be based on prior knowledge of the 1982 version. The critical changed features are:

1. 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 the 1982 theory (and many others) the distinction between fear and anxiety does not depend on the conditioned or unconditioned nature of stimuli used.

2. There are categorical behavioural and neural distinctions between panic (periaqueductal gray), phobia (hypothalamic/amygdala), anxiety (amygdala/septo-hippocampal system) and obsession (cingulate).

3. Anxiety is seen 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.

4. Perhaps the most fundamental change is that the BIS is viewed as being distributed among a number of neural structures with, in particular, aspects controlled by the septo-hippocampal system and the amygdala, respectively, that can be doubly dissociated. The 1982 theory views anxiety as largely depending on a single structure; the 2000 theory views it as depending on a coherent, hierarchical, system of structures. The present theory expands the systems further and views anxiety and fear as depending on parallel, symmetrical, hierarchical systems of structures.

5. Similarly, the functions of the septo-hippocampal system are distributed across the nominal psychological functions of anxiety and memory. This dual aspect of BIS output was inherent in the 1982 theory but is more explicit and elaborated in the 2000 theory. It will not be dealt with further in this paper (which focuses on anxiety) but specific application of our theory to the role of the hippocampus in associative memory is provided elsewhere [105]. However, briefly, it rests on the evidence that anxiolytic drugs affect ‘hippocampal’ tests of memory [102,103,153,154] and that so-called ‘amnesia’ in humans is in reality ‘hypermnesia’. Associative memory systems of the brain necessarily throw up multiple alternative correct choices, particularly in high interference task or with reversal of a learned discrimination, without the hippocampus the conflict between items cannot be resolved and so either no choice, or an incorrect choice, is output. This pandemonium is predicated to exist prior to conscious awareness (with amnesia being analogous to the ‘tip-of-the-tongue’ phenomenon where an item of information is temporarily irretrievable).

Before proceeding it is particularly important to emphasise two points: that the conflict that activates the BIS is one between goals experienced by the subject rather than inherent in a paradigm; and that although termed ‘the behavioural inhibition system’, the BIS is, and has always been, postulated to generate additional outputs related to attention and arousal.

Let us first consider conflict (see Gray and McNaughton, 2000, Appendix 1 and 8). 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 passive avoidance—which might be thought to be the quintessence of behavioural inhibition. For example [123], rats with septohippocampal lesions showed no passive avoidance deficit in a running wheel in which there was little spontaneous running—except if they were first trained on a contrary active avoidance response. Likewise with ‘conditioned suppression’ in which 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” (Graeff, pers. comm, see also Graeff, this issue). However, conditioned suppression appears to be insensitive to anxiolytic drugs unless the conditioning takes place in the same apparatus as the operant testing and together with a range of other data (Gray and McNaughton, 2000, Appendix 1 and 8) this suggests that contextual conditioning results in approach-avoidance conflict and, in particular, eliciting defensive quiescence (that, unlike freezing proper) is sensitive to anxiolytic drugs [107].

Let us now consider elicitation of behaviour by the BIS. The BIS inhibits prepotent behaviour (i.e. both approach and avoidance) but elicits, e.g. exploratory, behaviour designed to resolve the conflict. This elicitation is particularly obvious in the Blanchard’s work with rearing and a range of related anxiolytic sensitive behaviours characterising intermediate levels of defensive approach. Defensive burying is a particularly characteristic anxiolytic-sensitive behaviour that has been extensively studied by Treit and colleagues [44,60,108–110, 156,157]. In the ‘shock-probe burying test’, an electrified probe shocks rats 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” [8]. Thus, burying fulfils our major criterion for an anxiety-related reaction in that it involves approach to a source of potential threat.
2. Anxiolytic drugs as markers for systems involved in anxiety

Drugs must act on specific brain structures if they are to change specific emotions. Suitable alterations in those target structures should, then, produce subsets 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.

2.1. The septo-hippocampal system

The core of the 1982 theory was based on the extensive similarities between the behavioural effects of anxiolytic drugs and hippocampal lesions. By 2000 this similarity was shown to be true of novel anxiolytic drugs. These drugs do not interact with the GABA\(_\text{A}\) receptor and so do not share shown to be true of all classes of anxiolytic drug, including those (like classical anxiolytics [27–29,99,166–173]. A further link that anxiolytic drugs produce characteristic changes in memory function of the sort typically attributed to the hippocampus.

The core of the 1982 theory was also based on 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 antidepressants) that have no overlapping side effects with classical anxiolytics [27–29,99,166–173]. 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 [163]. The drugs appear, then, to prevent the formation of new threatening memories leaving old ones intact. This is a parallel to the anterograde rather 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. However, recent data have shown that intracranial anxiolytic injections can concurrently change hippocampal theta and behaviour as extensively as systemic injections [164]. Importantly, when theta frequency is specifically changed by intracranial injections, formation of spatial memory is changed to an equivalent extent [124].

It is important to emphasise that our inclusion of a structure within the distributed network that is the BIS does not imply that its functions are limited to its role in the BIS. 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 more cognitive conflict resolution more to the entorhinal cortex and more 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 (see Bannerman et al, this issue).

2.2. The amygdala

For many, a glaring omission from the 1982 theory was the amygdala. However, at that time, this structure (or better, set of structures) seemed involved in avoidance in general 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 positive and negative instances) than those between anxiolytic action and amygdalar lesions [69]. However, since 1982 it has become well accepted that the amygdala is involved in the control of both fear and anxiety [88]. In particular, anxiolytic drugs of all chemical classes act directly on the amygdala to reduce the arousal associated with anxiety [36], and this arousal is not mediated by the septo-hippocampal system [106].

We are faced, then, with an amygdala that appears to mediate some but not all aspects of anxiolytic action; a hippocampus that appears to mediate some but not all aspects of anxiolytic action; and significant overlap in the behaviours controlled by each. Previous theories have tended to favour a more unitary view of the amygdala. On the one hand, Gray and McNaughton (2000) concentrate on the role of the amygdala in anxiolytic-insensitive tasks to such an extent that in one figure (Fig. 11.1) they locate anxiolytic-sensitive arousal within a set of structures that they characterise as anxiolytic insensitive. On the other hand, LeDoux [88] concentrates on the role of the amygdala in defense to such an extent that he treats the role of the hippocampus as equivalent to that of perceptual and associative areas of neocortex, ignoring its involvement in innate behaviours, its relationship to anxiolytic action and the effects of anxiolytics on its functioning.

We resolve these issues here by emphasising the complexity of what is termed ‘the amygdala’. The amygdala is a set of structures, the boundaries of which are not well defined and that may include the ‘extended amygdala’ [39]. Even within the classic ‘amygdala complex’ there are some nuclei that cytoarchitecture would classify as subcortical and others that it would classify as cortical. It is an area, then, with a number of structures operating at a number of levels. Some parts of the amygdala also appear to have special anatomical relationships with some parts of
the hippocampal formation. The term ‘amygdala’ can even be viewed as a set of distinct structures rather than being a unitary entity with multiple parts [151]. We argue, then, that some parts of ‘the amygdala’ are functionally distinct from other parts—particularly with respect to their involvement in anxious action. We will leave the details of this suggestion to the final model presented below - but it should be noted that we have as yet made no detailed specific assignments of parts of the amygdala to specific functions nor linked such assignment to the known interconnections of the parts. A final caveat in discussing the amygdala must be that to assign it a role in anxiety (as well as fear) is not to ignore its known role in many other emotions, including affectively positive ones.

2.4. Overview of the neural structures involved in fear and anxiety

The above discussion has highlighted only those structures whose role we will present in a different light than Gray and McNaughton (2000). There are many others in the model given below whose inclusion and function have been justified previously in the control of both fear and anxiety [36,43,58,69,88].

The structures included in the model range from the prefrontal cortex to the periaqueductal gray. The conclusion we now wish to draw from our discussion of the amygdala, medial hypothalamus and PAG is that fear and anxiety (as categorically distinct entities) are represented at all levels of these systems. However, the involvement of medial hypothalamus and PAG in anxious action is sufficiently minor that it was essentially overlooked previously [69]. Equally, we will argue below for a functional distinction between fear and anxiety that would make fear more likely to be engaged with more immediate threats and anxiety more likely to be engaged under conditions of distant or anticipated threat. In the hierarchical model of defense systems present below, therefore, we present 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.

A final extension of the theory of Gray and McNaughton (2000) is the role of the cingulate and prefrontal cortices. These were treated indeterminately and more specific allocation of their functions will be dealt with below after presentation of the overall model.

3. Constructs for a theory of fear and anxiety

We will summarise here some critical constructs that are used by us, following Gray and McNaughton (2000), in a quite specific and rigid fashion. These constructs, taken together with the minor modifications in the neural aspects of the theory described above, then produce our two dimensional view of defence.

3.1. Reward and punishment

The theory [65,69] views substantive affective events as falling into just two distinct types, positive and negative. Rewards and punishments are treated as separate homogenous classes as in most other theories. It also views the absence of an expected positive event as functionally the same as the presence of a negative event and vice versa [62]. Rewarding events and the omission of punishing events are viewed as operating via a Behavioural Approach System (BAS), see below.

Although this paper focuses largely on defensive approach and defensive avoidance, it should be noted that
we hold that the BIS is engaged by any type of conflict, not only approach-avoidance conflicts. Thus defensive approach 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.

3.2. Fear and Anxiety—defensive direction

The theory views fear and anxiety as distinct, and in some respects opposite, entities. This distinction is clearly made only in the 2000 version of the theory and is converted into a core construct in the present paper and is extended to assume symmetry of the systems controlling fear and anxiety. The categorical separation of fear from anxiety derives from detailed analysis of defensive responses by Robert and Caroline Blanchard [9,12–15].

The Blanchards link to a state of fear a set of behaviours elicited by a predator. These behaviours, originally defined ethologically, turn out to be sensitive to drugs (see Table 1) that are panicolytic but not to those that are only anxiolytic [15]. The Blanchards link to a state of anxiety a quite different set of behaviours (especially ‘risk assessment’). These behaviours, again defined ethologically, are elicited by the potential presence of a predator and turn out to be sensitive to anxiolytic drugs. The Blanchard’s detailed analysis, and its pharmacological validation, provides a basis for coherent conceptualisation of a vast animal literature. For example, their analysis of fear predicts the well-demonstrated insensitivity to anxiolytic drugs of active avoidance in a wide variety of species and of phobia in humans [140].

However, because of the detailed effects of anxiolytic drugs on behaviour [64], we hold that the key factor distinguishing fear and anxiety is not that posited by the Blanchards, namely immediacy (or certainty) versus potentiality (or uncertainty) of threat. Rather the critical factor is what can be called ‘defensive direction’. 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). 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.

Table 1

<table>
<thead>
<tr>
<th>Class</th>
<th>Novel</th>
<th>IMI</th>
<th>CMI</th>
<th>MAOI</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple phobia</td>
<td>0*</td>
<td>?</td>
<td>0</td>
<td>?</td>
<td>(–)</td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0?</td>
</tr>
<tr>
<td>Social phobia</td>
<td>–</td>
<td>(–)</td>
<td>0</td>
<td>(–)</td>
<td>–</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>0*</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Obsessions/compulsions</td>
<td>0</td>
<td>(–)</td>
<td>–</td>
<td>(–)</td>
<td>–</td>
</tr>
<tr>
<td>Unipolar depression</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Atypical depression</td>
<td>0</td>
<td>?</td>
<td>(–)</td>
<td>?</td>
<td>–</td>
</tr>
</tbody>
</table>

Various classes of drugs effective in treating neurotic disorders and their relative effects on different neurotic syndromes. Exceptional effects of individual members of a class are ignored (e.g. the antidepressant and panicolytic actions of specific benzodiazepines such as alprazolam). It should be noted that antidepressant monoamine oxidase inhibitors, in particular phenelzine, are like novel anxiolytics such as buspirone and also tricyclic drugs such as imipramine. They all have separate anxiolytic and antidepressant 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 generalised anxiety. Key: class, classical anxiolytics such as benzodiazepines, barbiturates and meprobamate; CMI, Clomipramine; IMI, imipramine and closely related tricyclic antidepressants; 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 disparate effects. From McNaughton [98] With additions from Stein et al. [146].

* Ref. [140]
* Excluding alprazolam. Ref. [139]
* Ref. [94]

3.3. Defensive distance

The theory views defensive behaviour as resulting from the superimposition on defensive direction (i.e. approach or avoid) of ‘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 operationalises an internal cognitive construct of intensity of perceived threat. It is a dimension controlling the type of defensive behaviour observed. 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 (Fig. 1A). Thus, defensive distance maps to different levels of a Fight/Freeze/Flight System (FFFS).

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 face to face 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 (Fig. 1B), defensive quiescence occurs at the closest defensive distances (and, in rats, can be distinguished from freezing only by minor postural features). At intermediate distances, risk assessment behaviour occurs and, at very great distances, defensive behaviour disappears and normal pre-threat behaviour reappears.

It is crucial to note here that anxiolytic drugs affect defensive distance 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 Fig. 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 Fig. 1B), an anxiolytic drug will decrease risk assessment (which again increases approach to the source of threat). Thus, the drug does not alter specific observable behaviours consistently but produces changes in behaviour that are consistent with an increase in defensive distance [10,11].

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, in preparation). 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.

Trait anxiety, in this sense, would represent a specific risk factor for generalised anxiety disorder that would be quite independent of risks for panic disorder, obsessive-compulsive disorder or depression. (Anxiolytic action does not entail change in any of 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 Fig. 1B (but not Fig. 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) 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 Fig. 1A can be used to indicate the types of defensive avoidance behaviour elicited by different perceived 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 (Corr and McNaughton, in preparation).

So far, we have discussed threats that should be avoided (defensive avoidance). These can produce different behaviours depending on whether the threat can be avoided or not (Fig. 1A). We also discussed threats that should be approached but which in principle can be avoided. Indeed, the whole purpose of risk assessment behaviour (Fig. 1B) is to allow approach to occur while avoiding the consequences of a perceived threat. There remains a further possibility (Fig. 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” is based but we have tentatively identified it with depression [95].
The 2000 theory holds that anxiety results from conflicts between competing available goals. The classic form of such conflict (Miller, 1944 [113]; see summaries by Kimble, 1961, pp. 452–57 [83]; Gray, 1987, pp. 140–147 [66]), and the most familiar for those studying anxiety, is approach-avoidance [97]. 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. Nonetheless, we will concentrate on approach-avoidance conflict for the sake of simplicity.

Once conflict, in the sense of a close balance between competing goals, is detected, there is a selective potentiation of the cognitive 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 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.

These jigsaw pieces appear complicated taken one at a time. But they can be assembled into a coherent, two-dimensional whole that is simpler than the sum of its parts.

4. The two-dimensional defense system

The hierarchy of defensive behaviors (mapped to different defensive distances) proposed by the Blanchards was linked to a matching neural hierarchy by Deakin and Graeff [43,58]. The 2000 theory expanded these ideas to two dimensions by adding the concept of defensive direction. The present paper extends these concepts: (1) by segregating the structures controlling defensive approach and defensive avoidance into totally distinct parallel streams; (2) adding medial hypothalamus and PAG (see above) as lower level components of the system controlling defensive approach and so achieving symmetry of the parallel systems; (3) applying the concept of hierarchy plus additional data so as to assign tentative functions to the cingulate and prefrontal components of the defense system (see Fig. 3).

Fig. 3 is divided into two halves, with various aspects of fear controlled by the structures on the left and various aspects of anxiety controlled by the structures on the right. At the bottom of the figure are the lowest (most caudal, subcortical) neural structures at the top are the highest (most rostral, cortical) neural structures. This is a two dimensional variant of the hierarchical organisation proposed by Deakin and Graeff [43].

The neural hierarchy corresponds to a functional hierarchy. The bottom of the figure represents the smallest defensive distances and the top the greatest. There is then a corresponding mapping of symptoms (and also syndromes, see below) to structures. It should be emphasised that, particularly with prefrontal cortex and cingulate cortex (which are vast and complex areas), any role we assign to them in the control of anxiety and fear does not exclude them from important roles in other emotions (as for the amygdala) or in more cognitive processing (as for the hippocampus). Our assignment is also, at present, less specific than is desirable. Particularly with prefrontal cortex, we not only do not specify specific parts to carry out specific functions but we clearly assign multiple complex functions to ‘prefrontal cortex’ that must each involve somewhat different parts of that structure.

4.1. Defensive avoidance

At the bottom left of Fig. 3, associated with the periaqueductal grey, we have undirected escape/panic then above this, in the medial hypothalamus, we have directed escape/phobic escape [43]. The amygdala controls active avoidance/phobic avoidance [36,88] but we have explicitly separated the components of the amygdala that deal with autonomic arousal and with active avoidance behaviour. We will discuss the reasons for this in Section 5.

Above the amygdala, we place the anterior cingulate and assign to it 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 defense. Anterior cingulate is involved in the perception of pain [25,26,33,34,85], the production of anger [48], Pavlovian fear conditioning [84] and avoidance learning [86]. Likewise, anterior cingulate lesions impair avoidance of the CS-in discriminated autoshaping, as well as “lick suppression during the presentation of a CS + that had previously been paired with shock…; and active avoidance learning” [18].

Anterior cingulate cortex thus deals with fundamental outputs of the FFFS— but involves stimulus inputs that may be as complex as guilt [141] with a focus on the affective rather than sensory aspects of pain [132]. In particular, we see the anterior cingulate as controlling active avoidance behaviours that include those that cannot be terminated by safety signals. Hand washing to avoid infection is an example. We thus assign their pathological form, obsessive compulsive disorder, to the anterior cingulate [50,133]. 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 aspects). 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 Fig. 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 [133].

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 [91,135] and in more general response conflicts ‘in which a prepotent response tendency has to be overcome’ [7,19]. Indeed, there is evidence that it is more involved in conflict monitoring than in selection for action [17,23,24]. These data would, nonetheless, be consistent with our assignment of anterior cingulate to the active defense system if the tasks used (e.g. Stroop test) are in fact eliciting multiple responses [47] that conflict in the attempt to achieve a single goal.

Fig. 3. The two dimensional defense 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.
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 [69]. The inhibitory aspects of anterior cingulate function in avoidance may also relate more to the correct timing of responses held in working memory [57] and the coordination of response sequences [82,122,131] than to conflict per se.

There is also evidence that anterior cingulate is involved in the generation of mania [16] and in Pavlovian reward conditioning [126]. 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" [18]. 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 [45,127] and different parts appear to be involved in more cognitive and more emotional processing, respectively [87,152,162]. Defensive approach and defensive avoidance may then be represented in both anterior and posterior cingulate systems [57] rather than, as we suggest here, distributed between them.

At the top left hand of Fig. 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 (Fig. 4) components of the BAS with cells that are sensitive to the valence and value of reinforcement or related behaviours [121,128,130] including positive sensations [55]. But we have insufficient evidence at present to subdivide 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 [114]. 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 obsessioanal issues [129] and that abstract forms of punishment (e.g. monetary loss) appear to be represented in the ventral stream of frontal cortex [121]. There are some indications that BIS output (possibly from the dorsal trend of the prefrontal cortex, see below) suppresses activity in the ventral trend [143,144].

For both cingulate and frontal cortex it should be emphasised that, while we assign to parts of them specific defensive functions, this in no way implies that all or much of these structures is devoted to defense as opposed to other affective systems or to emotion as opposed to cognition. Equally, as discussed earlier, the topographic mapping between prefrontal, hypothalamic and PAG structures implies a differentiation between strands of defense reactions that adds extra dimensions such as escapability versus inescapability [4,6,95] that are not considered here. Finally, for simplicity, we have represented the levels of the system as reciprocally connected with each other. But, in practice, the prefrontal cortex, for example, can influence the PAG directly [1,53,142], maintaining the topographic organisation of more indirect connections. There will be similar bypassing of levels between all parts of the system.

4.2. Defensive approach

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. ‘Fear’ of the dark, by contrast, involves entry into the threatening situation and requires continual checking for sources of
potential danger with no explicit avoidance response being available.

For the same reasons as given above for active avoidance, then, we postulate a control of very high level passive avoidance behaviour and risk assessment by the dorsal trend of frontal cortex. Although phrased in terms of approach-avoidance conflict we also see the dorsal trend as resolving approach-approach conflicts as evidenced by reductions in interference [91]. It is noteworthy that cells in the dorsal (as opposed to the ventral) trend of prefrontal cortex are sensitive to the context of reinforcement [161]. The dorsal trend could, therefore, involve a variety of ‘deep’ forms of obsessiollarity and other complex anxieties, in particular, social anxiety1.

Social behaviour is sufficiently complex that different aspects of it must be controlled at multiple levels of the defense 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 [3,56,120,158].

Similar results have been obtained with anxiety (and cortisol increases) induced by maternal separation both acutely in Rhesus monkeys [136] and chronically in human infants—“a pattern of activity that might be a correlate of trait-like anxiety … the similarity of the activation patterns [with state and trait anxiety] is noteworthy” [136]. Given the complexity of prefrontal cortex there must be a range of other high level/obsessional forms of anxiety to be described.

‘Fear’ of the dark, however, is likely to be at a lower level than prefrontal cortex and, assuming symmetry with simple active obsessions, would be likely to be controlled by posterior cingulate cortex. Fear of the dark can 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 [30,31,70,74,135,150] although its exact involvement and the contribution of fibres of passage remains to be determined [111,117,118,160]. A related form of anxiety is agoraphobia (which, in the theory would be better named as agoranixiety). 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 defense 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 rather than 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 much agoraphobia is the result of conditioning to prior pathological panic (primarily controlled by the periaqueductal grey). Space 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 [92]. Consistent with our linking of posterior cingulate to hippocampal function it appears to deal with more long term encoding of information as compared to anterior cingulate which appears to deal with shorter term encoding [57] and to contribute to dysfunction in dementia [78,79,93,115]. It is noteworthy here that spatial dysfunction resulting from posterior cingulate damage, like hippocampal amnesia, is anterograde but not retrograde [80].

Below the posterior cingulate 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. To it we attribute cognitive aspects of conventional anxiety and generalised anxiety disorder [96]. However, as we noted above the arousal associated with anxiety is controlled by the amygdala [36] not the septo-hippocampal system [106]. 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 generalised anxiety disorder. One, more hippocampally centred, 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 [69]. Equally, active avoidance involves equivalent effects on cognition and arousal that are not sensitive to anxiolytic drugs. This is the basis for the 3 different boxes labeled ‘amygdala’ in Fig. 3. Further work is required to precisely identify the different neural components of the amygdala corresponding to each.

Immediately below the amygdala is the medial hypothalamus (which like PAG shows some sensitivity to anxiolytic drugs). By analogy with the active avoidance system, and in contrast to earlier versions of the theory, we postulate that this would control the simplest behaviouiral reactions on entering a situation in which fairly immediate danger is faced. We speculate that this would involve, in particular, simple forms of risk assessment.

At the bottom right of Fig. 3, we assign a role to the PAG in the lowest levels of control of anxiety. We linked active freezing, above, with panic. Given the defensive quiescence (akin to, but posturally distinct from, freezing) generated by anxiety, we postulate a passive form of ‘anticipatory panic’ that would be generated by a high level of anxiety that, nonetheless did not elicit escape - and this would be likely to

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1 This suggestion and the literature we quote in the following paragraph were provided by Dr Caroline Bell.
be linked to the anxiolytic-sensitive anticipatory hypopalgesia mentioned earlier.

4.3. An overview

The key feature of our present view is that, independent of the precise details suggested above, defensive distance maps onto a series of distinct neural modules, to each of which is attributed 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.

The view of the defence system as partitioned into distinct components that can be modulated by more global systems was developed largely on the basis of animal experiments. But the linking of this view to terms such as panic, phobia and obsession is based on the clinical effects of drugs. As shown in Table 1, 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 defense system.

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 defense system (Fig. 2). Drugs such as imipramine or specific serotonin reuptake 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 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 [41].

The more restricted profile of buspirone in comparison to imipramine can also be understood in terms of this model. Buspirone acts as an agonist on 5HT1A receptors. At such receptors it will have the same effect as imipramine. Buspirone simulates the effect of 5HT on the receptors, imipramine increases the amount of 5HT that can act on them. Imipramine has more general effects because it increases the availability of 5HT quite generally. It thus acts as an agonist not only on 5HT1A receptors but also on all of the very large number of other 5HT receptors.

The action of buspirone may be even further limited. Its effects are not identical to those of other 5HT1A acting drugs. It may act only on a subset of 5HT1A receptors or it may have additional actions, for example on the pituitary adrenal system [104], that interact with its primary action. The key point, for our current purposes, is that many of its actions are similar to those of classical anxiolytics and where the various drugs differ we can argue that there are different underlying neural systems that are differentially affected.

It should be noted here that the genetic influences on the 5HT system that have been identified so far in humans, and could easily underlie personality factors, operate to alter the system generally rather than impacting on specific receptors. Variance in personality would then be expected to be similar to the variance produced by a drug such as imipramine rather than a drug such as buspirone.

So, comparison of drug classes can be used to dissect out different parts of the defense system. But this comparison must involve several different drugs within each class if specific conclusions are to be drawn about specific brain systems.

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 specialised modules are general modulatory systems. It would be expected, and seems to be the case, that it is these latter modulatory systems that are crucial for personality.

Both serotonergic [41,43,145] and noradrenergic [101] systems have diffuse modulatory input to essentially the whole defense system, as well as to additional parts of the cortex and subcortex. Only the serotonergic system is shown in Fig. 3. An important feature of its modulation of the defense system is that the lowest level (panic) is suppressed by input that activates higher levels. This results not only in differential effects of drugs but also in such apparently anomalous phenomena as relaxation-induced panic [58].

There are a number of important points to note about this neural architecture if the distinctive aspects of the theory are not to be misunderstood:

1. Fear (as defined by the Blanchards, i.e. involving all behaviours directed towards defensive avoidance) is mediated by a system involving the anterior cingulate, amygdala, medial hypothalamus and periaqueductal gray. The nature and operation of this system with respect to fear, as opposed to anxiety, is that generally accepted [36,43,88]. Fear-related behaviours
(e.g. active avoidance) and hence the parts of these structures mediating fear, are not sensitive to anxiolytic drugs. So, although 5HT innervates the whole defense system, 5HT1A receptors appear critical only for the defensive approach system.

2. The ‘adequate inputs’ to this system are best described as the detection of threat. Stimuli, per se, are not critical. It is the ‘meaning’ effectively attached to those stimuli by perceptual systems that determines the response. This involves multiple parallel processes: some ‘quick and dirty’ operating in an essentially reflexive fashion, others ‘slow and sophisticated’ operating to cancel or augment the quick and dirty responses as appropriate - or to generate a response if none has yet occurred [88]. The slow and sophisticated processes would normally be referred to as cognitive processes but their operation is no different in principle, although more complex in practice, than more ‘reflexive’ responses.

3. Where anxiety (i.e. conflict) involves approach to a source of fear, but not frustration, the amygdala is involved both as the target of threatening stimuli and as the site on which the BIS (septo-hippocampal system) operates to increase the valence of those threatening stimuli and so increase behavioural inhibition.

4. The amygdala is the site through which the BIS increases arousal. For this output of the BIS, the septo-hippocampal system is not involved and the amygdala is the location at which anxiolytic drugs act directly [35,37,38]. This aspect of amygdala function is also distinct from the anxiolytic-insensitive control of fear (note the two ‘amygdala’ boxes in Fig. 3). We will discuss it in more detail below.

5. Anxiolytic drugs act directly on a range of sites (supramammillary nucleus, locus coeruleus, raphe nuclei) to alter indirectly septo-hippocampal function and so behavioural inhibition. Recent data also suggest that genetic variation can alter behavioural inhibition by altering the sensitivity of receptors within the septo-hippocampal system itself [32]. Such direct action on the hippocampus is highly compatible with the 2000 theory but was not included within it.

6. Under ecologically normal conditions, control of skeletal behaviour will pass rapidly between the FFFS and BIS depending on the direction the organism is moving. In special paradigms, such as two-way active avoidance, both systems can be engaged simultaneously (with the result that anxiolytic drugs improve two way active avoidance by suppressing a competing passive avoidance component). This concept is difficult to deal with when one believes that the experimenter controls the paradigm. We like to think we have constrained an organism to the task we have set. In practice, our paradigms are constrained by the way the organisms respond.

5. The 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 by 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 (Fig. 4).

Gray has previously [67,68] 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’ [68]. Such caudate motor command subroutines are quite distinct from the affect-laden goals that are the subject of the FFFS, BAS and BIS [69]. 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 system instantiates the BAS is consistent with its involvement in appetitive arousal, facilitation of reward processes, and flexible response sequences including approach to safety signals [77]. 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 [46].

6. The BAS, FFFS and BIS

The left-hand side of Fig. 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 Fig. 5 represents this entire system.
The right hand side of Fig. 3 describes the machinery of the BIS and is, again, represented by a single box in Fig. 5, as is the BAS.

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 (Fig. 5) include not only inhibition of avoidance 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 (Fig. 5), it does not decrease the motivational aspects of fear or frustration. Rather, the normal resolution of conflict by the BIS involves 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 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 value by associated reward is symmetrical. It is independent of whether a response is required, and does not involve the BIS since it is not affected by anxiolytic drugs [100].

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 [49]. The opposite interactions of the FFFS and BAS in decision-making and on arousal are shown in Fig. 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 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

![Fig. 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.](image-url)
The BIS has three distinct effects: it suppresses approach and avoidance; it increases the tendency to avoid (lower BIS arrow in Fig. 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 Fig. 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 Fig. 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 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.

7. Experimental tests of the theory

An important conclusion of our theory is that it should be possible to separate different syndromes of defensive disorder by using theoretically based challenge tests and so bypass the problem that (given the interconnectedness of structures) different syndromes can present with much the same symptoms. Indeed, a key feature of the tests we propose is that they should seldom be directed towards the most obvious symptoms and should be administered when state anxiety and hence symptoms are minimal. The same would of course be true of any challenges used to activate the brain for imaging.

The central idea behind our suggestions for differential diagnosis is that the specific nodes of the defence system should be selectively challenged to determine whether they are functioning normally. Such challenges should be designed to produce minimal reactions from the rest of the defence system. Otherwise, anxiety (or fear or panic) will automatically spill over into activation of much of the remainder of the system, so making it impossible to determine at which point excessive reactions begin.

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2 The suppression of conflicting behaviours is quite specific. Not only does conflict encourage risk analysis behaviour but 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.

3 Text taken with minor modifications from Gray and McNaughton (2000), Chapter 11, Section 20
An important corollary of this recursiveness (and an idea gradually creeping into conventional diagnosis) is that comorbidity is likely to be extensive. For there is little reason to suppose that just one node of the overall defence system should often be the only one over-reactive in any one individual at any one time.

Let us now look at some possible challenge tests and ways in which they might be put together to form a diagnostic scheme (and used directly to test some aspects of the theory).

Starting at the bottom of the defence system with the periaqueductal gray, what we require is a stimulus maximally activating this region accompanied by minimal activation of other parts of the defence system. With such a challenge we could then test patients for the extent to which the periaqueductal gray itself is over-reactive, as opposed to being secondarily triggered by excessive activity elsewhere in the defence system. The periaqueductal gray, as noted earlier, controls ‘fight/flight reactions to impending danger, pain, or asphyxia’ [59]. ‘Danger’ in any general sense could clearly produce widespread activation of the defence system before activating the periaqueductal gray. To detect not only clinical panic disorder (which some define as involving activating the periaqueductal gray. To detect not only widespread activation of the defence system before ‘Danger’ in any general sense could clearly produce widespread activation of the defence system before activating the periaqueductal gray). As soon as panic is elicited, other parts of the defence system could contribute to the attack. More subtle assessment could be necessary; and, indeed, it seems that panic disorder may be detectable from irregularities in respiratory rhythm and perhaps the response to respiratory challenge (e.g. Papp et al., 1995 [125]). As soon as panic is elicited, other parts of the defence system could contribute to the attack. So, challenge with fixed levels of CO₂ is not only theoretically unattractive but does not discriminate panic well from, e.g., specific phobias [2]. Threshold measurements, on the other hand, should detect supersensitivity in the periaqueductal gray independent of other abnormalities in the defence system. There may also be relatively input-specific abnormalities of the periaqueductal gray whose detection would require testing with, say, painful stimuli or adrenaline challenge as well as asphyxia.

We have linked amygdalar dysfunction with the arousal component of anxiety. The most obvious relevant challenge would be fear-potentiated startle, since this is not only sensitive to anxiolytic drugs (including when injected into the amygdala), but is also insensitive to hippocampal lesions. One problem here would be if further work with animals were to show this test to be sensitive to hypothalamic or periaqueductal gray lesions (an issue which, to our knowledge, has not previously been investigated).

Next we come to the septo-hippocampal system. What is required is a test sensitive to septo-hippocampal system damage and anti-anxiety drugs, but not to amygdalar or periaqueductal gray lesions. The most obvious tasks, here, are spatial navigation, delayed matching to sample and behaviour on a fixed interval schedule of reward. Of these, delayed matching to sample can be most clearly set up in an anxiety-free form and so would probably be preferable, but it might be too specific in the aspects of septo-hippocampal function which it engages (Bannerman et al, this volume).

We have only limited clues as to what might constitute useful diagnostic tests for other anxiety-related disorders. There is ‘selective, subtle evidence of autonomic dysregulation’ in social phobics tested with autonomic challenges which did not include provocation of anxiety [147]; but more work will be required to show that this dysregulation is not also present, e.g. in panic disorder or agoraphobia. Similarly, tasks involving visual attention show abnormalities in obsessive compulsive disorder patients [119], but it will be necessary to show that this is not also the case in generalized anxiety disorder or as a simple consequence of anxiety. Tests of prefrontal hyperfunction could be based on the existing neuropsychological tests of prefrontal hypofunction.

8. Overview

Fig. 3 shows a two dimensional view of defense. The first dimension is an essentially categorical division between two systems: one controlling defensive avoidance (fear) and one controlling defensive approach (anxiety). One might ask, as did a referee of this paper, what is “the attraction of attempting 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 defense 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 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 distinguish them if we are to have a clear picture of the world - and some chance of ultimately being able to categorise genuine syndromes of defensive reactions.

The second dimension is an essentially hierarchical organisation both functionally (in terms of defensive distance) and neurally (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 categorising a multitude in terms of a simple, externally defined, dimension.

These two dimensions account for the differentiation between different defensive behaviours. Serotonergic and noradrenergic fibres that essentially mediate global threat sensitivity modulate all the structures controlling defense. The different levels of each system and the two systems as a whole are highly interconnected to allow parallel control by both ‘quick and dirty’ and ‘slow and sophisticated’ systems 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 time scales, underpinning therapeutic drug actions and providing the basis for personality variables that determine risk of morbidity.

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 [58]. Also absent is the highly detailed topographic mapping between the levels [4,72,137]. Each component of the model of Fig. 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 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 our account is only of acute reactions. Indeed, it is important to note that control can pass from one system to another in an instant. The reactions to chronic threats are different and controlled by distinct systems [41] as may be entities such as antisocial personality disorder [42].

Clearly, further revision and elaboration to this theory will be demanded by data in the future. But we believe that the picture we present shows the possibility of arriving at a coherent neuropsychological theory of fear and anxiety that links neural, pharmacological, ethological, behavioural, clinical and individual differences. Suggesting that such an enterprise is possible and producing the first full-scale attempt at such integration was the unique and fundamental contribution to modern neuroscience made by Jeffrey Gray.

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