Brain Mechanisms of Anxiety

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This paper suggests a mapping of elements of anxiety to a hierarchically organized set of neural structures. Panic attacks are viewed as occupying the lowest level controlled by the periaqueductal greay. Phobia is viewed as occupying the next level controlled, principally, by the amygdala. Anxiety proper (i.e. the anxiety which can exist in the absence of panic but which can also accompany panic) is controlled by the septo-hippocampal system which not only has descending links to the amygdala but also ascending links to prefrontal and cingulate cortex. Obsessions and compulsions are held to depend on activity in the cingulate cortex and basal ganglia respectively - and particularly on the reciprocal interactions between these structures. It is also assumed that they can occur independently of anxiety. While, on this view, anxiety proper is fundamentally associated with the septo-hippocampal system (and the monoaminergic afferents to it), the prefrontal cortex is also a key structure for the more cognitive aspects of anxiety.

A crucial point about this hierarchical system is that each level is *reciprocally* connected to the next, and the higher cortical levels have direct descending connections to the lowest levels. On this view anxiety disorders will often involve (but need not necessarily involve) a mixture of panic, obsession and anxiety proper. Further, superficially similar anxiety syndromes could, in principle, be produced by quite different aetiologies because of the strong dialectical links between the different levels of the system.

In discussing the brain mechanisms of anxiety, it might seem necessary first to discuss in some detail the nature of anxiety itself. However, the aetiology, psychology and treatment of anxiety are covered in other papers in this special issue and show that defining anxiety is a far from simple task. So, in this paper I will take the reverse approach. I will look at a number of brain mechanisms which it appears should be involved in anxiety, whatever one means by this term, and from the resultant neurology build a neuropsychology which could, in principle, provide a means of defining anxiety. In this, I hope to reverse the opinion of Strongman (this issue) that physiological analysis has not given us psychological insight. For reasons of space, I have also not attempted to present a proper review of the neurology of anxiety and, instead, have cited general review articles - chosen where possible for a non-technical approach.

The brain mechanisms supporting any psychological process cannot be studied in a theoretical vacuum so, having ducked the issue of providing a substantive definition of anxiety, there remains the question of providing a working definition. For this, I use two stratagems.

First, I treat the categorisation of DSM-IIIR as given. That is, I accept as a descriptive rather than analytical device that there is a group of disorders (and implied matching non-pathological states) labelled 'anxiety disorders' which can be subdivided symptomatologically into a number of types as described in DSM-IIIR. This is merely a starting point for the analysis and does not, as we will see, force us to accept that the DSM typology has a substantive neurological basis. To allow an easier transition between the human DSM-IIIR description of anxiety and the neurology of anxiety which has been studied mostly in rats, I will discuss how DSM relates to recent ethological analysis of defence systems.

Second, I treat the subject of the 'neurology of anxiety' as *including* those structures the functions of which are specifically altered by the 'anxiolytic drugs'. As will be seen, as a class, but not individually, anxiolytic drugs can be discriminated from anti-panic, anti-obsessive-compulsive and anti-depressant drugs. (It should be emphasised that this is my own view of the data and is by no means generally accepted.) The preliminary neurology I will describe, then, deals with only those brain areas affected in the same way by *all* anxiolytic drugs and which should, therefore, contribute to anxiety proper. However, as we will see, this description will also necessitate us discussing other, closely connected, areas of the brain which are thought to be specifically involved in the panic, phobia, obsessions and compulsions from which we will have distinguished anxiety proper.

The picture I will paint will be of a hierarchically organised system with panic and fear occupying lower levels; obsessions and some of the more cognitive aspects of anxiety

occupying higher levels; and anxiety proper occupying an intermediate level. These psychological levels map onto equivalent levels of the nervous system (Graeff, 1994; Le Doux, 1994). This neurology can also be embedded in a full blown neuropsychology based on Gray's (1982) model of the Behavioural Inhibition System, which we are currently revising (Gray & McNaughton, in preparation). However, for reasons of clarity and brevity, I have attempted to minimise the intrusion of our detailed theoretical views into the present paper.

Much of the work which I will describe has used rats as subjects. It may be questioned, therefore, how far it can be applied to human anxiety - which for many is a highly cognitive phenomenon. There are three answers to this. First, in evolutionary terms, human anxiety is almost certainly an elaboration of simpler but homologous processes in our progenitors. The study of anxiety in animals is therefore likely to give us a clearer idea of the basic systems present in humans and upon which cognitive elaborations may be built. As Darwin said, given "facts observed both with man and the lower animals ... the latter facts are preferable, as less likley to deceive us" (Darwin 1872, p 27). Second, in psychological terms, it can be demonstrated that rats have many of the complicated cognitive capacities we ascribe to humans - but usually in a less developed form (language is a major exception here). In particular, it has been shown that stress and anxiety in rats depend on the animal's evaluation of stimuli rather than the physical nature of the stimuli themselves. Thirdly, I would argue that, at the end of the day (or hopefully of this paper) a non-human perspective on human anxiety gives us better understanding of what we mean by anxiety and of the way it works than we had before.

Anxiety and DSM-IIIR

Anxiety is defined in DSM-IIIR as

> 'apprehension, tension, or uneasiness that stems from the anticipation of danger, which may be internal or external. Some definitions of anxiety distinguish it from fear by limiting it to anticipation of a danger whose source is largely unknown, whereas fear is the response to a consciously recognized and usually external threat or danger. The manifestations of anxiety and fear are the same and include motor tension, autonomic hyperactivity, apprehensive expectation, and vigilance and scanning.
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> Anxiety may be focused on an object, situation, or activity, which is avoided (phobia), or may be unfocused (free-floating anxiety). It may be experienced in discrete periods of sudden onset and be accompanied by physical symptoms (panic attacks). When anxiety is focused on physical signs or symptoms and causes preoccupation with the fear or belief of having a disease, it is termed hypochondriasis'
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> (DSM-III-R, 1987, p 392).

Two key features of this definition for our present purposes are a) the possible requirement of distinguishing fear from anxiety; and b) the central position given to danger or threat in the definition of both anxiety and fear. Our first step, then, will be to look at ethological and pharmacological analysis of behavioural responses to threat in animals. This will allow us to partition defensive reactions in a hierarchical fashion as a precursor to assigning specific components of this hierarchy to specific brain systems.

The ethopharmacology of anxiety

Many purely psychological or pharmacological approaches to anxiety in animals suffer from the problem that 'for neither of these ... strategies is the functional unity of the actual behaviours measured apparent, nor is there a suggestion of any other obvious unifying factor except for those built into the selection procedures' (Blanchard and Blanchard 1990, p 125). The solution to this problem is that of ethological analysis: the analysis of behaviour in a natural or quasinatural situation which allows the functional significance of elements of behaviour to be determined. The Blanchard's have been working on this topic for some years in Hawaii which has provided them, through capture, with a source of wild rats - the defensive behaviour of which has not been altered by laboratory breeding programs. They have analysed the responses of these rats to entities which are innately perceived by these rats as predators, particularly humans (whose behaviour, unlike that of other predators can be carefully controlled).

Put very briefly, the Blanchards have found that defensive behaviours can be divided into a number of classes based on what they term defensive distance (which for most purposes can be treated as actual physical distance) and on features of the situation such as whether a threat is escapable or not and whether the danger is clearly present (as when a cat is visible) or merely potentially present (as when there is the odor, but no other sign, of a cat).

At very close defensive distances freezing, fight and flight are produced. Both the fight and the flight in this case occur explosively in the context of freezing and are relatively undirected. With a larger defensive distance, freezing is produced if the predator is inescapable and flight in the form of directed escape if this is possible. These reactions are subject to less urgency and can therefore involve more sophisticated analysis of the situation and responses to it. Once rats have escaped into their home burrows (which in the Blanchards' laboratory are arranged with special lighting and cameras so that the rats can be observed even in what to the subjects is the dark) they indulge in a variety of behaviours which vary over time. Critically for our purposes, these ultimately involve a variety of risk assessment behaviours coupled with the inhibition of the normal activities (such as feeding or drinking) which they would have carried out in the total absence of the cat. ('Freezing' is neurally and pharmacologically distinct from this 'behavioural inhibition', but they are difficult to separate purely in terms of behavioural observation.)

From their extensive and detailed observations, the Blanchards then isolated a set of predator-elicited behaviours (from which they derived a 'Fear-Defence Test Battery', FDTB) and a variety of potential-predator-elicited behaviours (from which they derived an 'Anxiety Defence Test Battery', ADTB). These batteries consist of a number of specific experimental tests each involving only one

component of the original natural behaviour. A crucial point for our analysis below is that behaviours in the FDTB are essentially unaffected by anxiolytic drugs while behaviours in the ADTB are virtually all affected by anxiolytic drugs.

From this analysis we can distinguish at least three levels of control required of the animal. First, there is the behaviour required when it is face to face with a predator. Here there is little room to manoeuver, decisions must be made quickly, and the chances of survival are not good. Reactions to this situation can clearly be primitive, provided they are fast. This level can be equated, in many respects, with panic in humans. Second, there is the behaviour required when a predator is present, but avoidable. There is likely to be some room to manoeuver, decisions should be made expeditiously (but it is better to take time to make the right decision about the action to be taken); and the chances of survival are good. This level can be equated with fear and simple phobia in humans. Thirdly, there is the behaviour required when there are signs that a predator might be present but there is no certainty. Here, the animal could solve the predator problem by doing nothing (ie inhibiting its prepotent behaviours such as feeding and drinking) - except for the fact that it will starve if it does nothing for too long. The animal must then resolve a conflict between the behavioural inhibition required by the potential predator and the many behaviours (feeding, drinking etc) which will promote survival. This conflict can generate specific risk assessment behaviours as a means of determining whether approach or avoidance of food sources etc is the wisest course of action. This level can be equated with anxiety in humans.

A final level, not discussed by the Blanchards (or by Graeff or Le Doux whose work we will consider below), is when a source of danger must be guarded against in the absence of any sign that it is present. An example here would be the need to wash one's hands to avoid infection - where the 'predator' is an invisible micro-organism. This behaviour could be viewed as being like the simple avoidance responses produced by a visible predator. However, given the fact that the 'predator' can never be localised or identified (except by scientists in a laboratory) it is probably better to view it as an even more remote anticipation of danger than anxiety. This level can be equated with obsession in humans. With all of these terms (panic, phobia, anxiety, obsession) our treatment so far implies that the relevant states can occur in adaptive circumstances and they are pathological only if their intensity is inappropriate for the eliciting stimulus or if they interfere with adaptive responding.

Matching behavioural levels to neural levels

As detailed by Graeff (1994) and Le Doux (1994), we can match the levels of the behavioural hierarchy we have described to the levels of an equivalent neural hierarchy. Simple, essentially undirected, escape reactions, freezing and aggression are controlled by the periaqueductal gray in the centre of the brainstem. This is reciprocally connected to the medial hypothalamus which can be viewed as controlling more directed escape reactions. This, in turn, is reciprocally connected to the amygdala which can be viewed as controlling avoidance reactions. There is considerable evidence (see Le Doux, 1994) that long term potentiation, a change in synaptic strength, at single synapses within the amygdala is the basis for the association between a previously neutral stimulus and the avoidance response. Lesions of the amygdala impair all forms of avoidance learning and so, in this sense, the amygdala can be viewed as a crucial site for the neural encoding of fear. However, it should be noted that the amygdala also appears to be important for appetitive reactions as well as aversive ones, at least in those cases which are accompanied by strong responses of the autonomic nervous system (see e.g. McGaugh, et al, 1993).

The amygdala sends major projections to the hippocampal formation in the temporal lobe (and receives a modest feedback from it). In contrast to lesions of the amygdala or the hypothalamus or the periaqueductal gray, lesions of the hippocampal formation do not impair escape responses or active avoidance responses (ie cases where the animal can avoid an aversive event by making a simple response such as pressing a lever). However, lesions of the hippocampal formation do impair responding in a wide variety of conflict situations involving not only stimuli which warn of impending punishment if a response is made, but also stimuli which warn that a reward will be lost if a response is made. In all these respects, the effects of lesions of the hippocampal formation, or of the septum which, with the hippocampal formation, forms the septo-hippocampal system, are like the effects of anxiolytic drugs (Gray & McNaughton 1980; Gray 1982). Thus we can view the amygdala as coding fear in the most general sense and providing this as an input to the septo-hippocampal system which uses this as one of its sources of information for coding anxiety.

At this point, someone acquainted with neurology is likely to say "but surely the hippocampus controls memory not anxiety". We must, therefore, look briefly at what we mean by an anxiolytic drug, at what we mean by amnesia, and at the extent to which anxiety disorders might be consequent on some failure of normal memorial processes.

What is an anxiolytic drug?

For our purposes we can divide the drugs used to treat anxiety disorders into two basic classes: classical and novel anxiolytics. The classical anxiolytics are best represented by the benzodiazepines and include barbiturates, meprobamate and to some extent ethanol and delta-9-tetrahydrocannabinol, the active constituent of marihuana. All of these compounds act directly (but at different sites) on the benzodiazepine-GABA-chloride ionophore complex (Haefely, 1990) and all, as a result, are not only anxiolytic but also, to varying degrees, anticonvulsant, muscle relaxant, hypnotic and addictive. The novel anxiolytics are best represented by buspirone, a partial agonist at the 5HT1A receptor, and can be taken to include the tricyclic antidepressant imipramine. While these each have their own side effects (e.g, some at least are antidepressant), none of them share any of the side effects of the classical anxiolytic drugs. The only clinical effect which both novel and classical anxiolytics have in common is the reduction which they can produce in anxiety.

Given that drugs such as benzodiazepines and buspirone share clinically only the property of anxiolytic

action it is noteworthy that they also share the capacity to impair two quite independent aspects of septo-hippocampal electrophysiology (McNaughton and Sedgwick 1978; McNaughton et al, 1977; McNaughton, Richardson and Gore 1986; Coop et al 1990; Coop and McNaughton 1990; McNaughton and Coop 1991).

In this context it is interesting to note that we can distinguish pharmacologically between panic (which is not affected by buspirone), atypical and unipolar depression (which are not affected by most classical anxiolytics), obsessive-compulsive disorder (which is preferentially affected by clomipramine) and anxiety proper, particularly generalised anxiety disorder (which is affected by classical anxiolytics, buspirone and imipramine). (As noted above, this categorical distinction would not be accepted by all clinicians - for a review of the drug treatments best used for the different symptomatologies see Silverstone, this volume.) Thus, in the clinic, many of these different symptoms co-occur and invidividual drugs may affect several of them simultaneously. But, because of their differential pattern of pharmacological sensitivity, and for reasons which we will discuss later, they must be treated as resulting from neurally discrete systems and potentially resulting from discrete disorders.

What is amnesia?

In neurology texts, the hippocampus is usually presented as one of the key structures damage to which produces amnesia. The suggestion that anxiolytic drugs act on the hippocampus and that the hippocampus is a key structure for the coding of anxiety in the brain is equivalent, then, to saying that anxiety involves a hypermnesia. While to some extent this is probably true (see below) we need to treat the term 'amnesia' itself with some care.

Human amnesics (e.g. the classic case of H.M., see Ogden and Corkin 1991) have not in fact lost their memory. There is much information which they retain from the period before the damage which created their problems and there is much which they can learn even after the damage. There are many current theories of the hippocampus which are distinguished by the different 'types' of memory which they see the hippocampus as supporting - but none is generally accepted over the others and none fit all the available data. Our view (Gray and McNaughton, in preparation) is that the amnesics' problem is not a failure to form new memories of any particular class but a failure to inhibit the formation of undesirable memories (largely as a result of a failure to increase negative evaluations). In this, we view the memory problems of humans and animals with hippocampal damage as being a special case of a more general failure to resolve conflicts (e.g. the approach-avoidance conflict of the rat in its burrow which, above, was described as being paradigmatic for the generation of anxiety). These issues cannot be dealt with in the current paper but we can provide some reasons for treating the effects of anxiolytics drugs as being qualitatively, if not quantitatively, similar to the effects of hippocampal lesions.

First, let us consider results with the Morris Water Maze. This is a circular tank filled with water in which a rat must find a submerged platform. Rats swiftly learn to go straight to the platform using spatial cues in the room. Hippocampal lesions produce a major deficit in this task (Morris et al, 1982) and it has been used extensively in recent years as a key test of the integrity of the septo-hippocampal system. We have shown that both classical and novel anxiolytic drugs impair spatial learning in the Water Maze (McNaughton and Morris, 1985; 1992) although the drugs are without effect once the task has been learned (McNamara and Skelton, 1991). This latter result matches the limited retrograde amnesia seen in humans with hippocampal damage.

Second, let us consider delayed matching to sample. This is a classic non-spatial test of memory in which the subject is presented with a stimulus, followed by a delay interval which can be varied and then by two sample stimuli from which they must select the one previously seen. In pigeons, and in rats performing a conditional form of this task, anxiolytic drugs impair performance on this type of task (Watson, 1989; Tan et al, 1990) and they do so in the same way as patients with Senile Dementia of the Alzheimer Type (Money et al, 1992) whose memory deficits can be attributed, at least in part, to hippocampal damage.

We have every reason, therefore, for treating amnesia as a failure of something other than 'memory' as such and for treating the effects of anxiolytic drugs, at least in rats and pigeons, as producing in a mild form this same 'amnesia'.

Is anxiety a memory disorder?

We have so far adduced a number of reasons for associating anxiety with the septo-hippocampal system and for seeing this system as a critical one for the effects of the anxiolytic drugs. The question then arises as to whether generalised anxiety disorder, for example, might involve some alteration in the processing of memories.

The brief answer is yes (see Eysenck, 1992; Eysenck and Calvo, 1992; Mathews 1993; Mathews and MacLeod, 1994), and this is not the place to go into the precise details of this involvement. Suffice it to say that we can view anxiety as involving certain biases in the processing of information which would, indeed, impact on what is stored (see McDowall and Allison, this issue). The septo-hippocampal system would, on the view presented above, be a critical site for generating this bias while not being the place that the information is ultimately stored. Equally, this same biasing of information by the hippocampal system, while important for memory under some circumstances, should not be viewed as exclusive to it and, for example, would be critical in providing appropriate negative bias during the resolution of innate (as well as learned) approach-avoidance conflicts.

Commenting on an earlier draft of this paper Peter Joyce of the Christchurch School of Medicine remarked that 'it is perhaps surprising that [you] did not mention Post Traumatic Stress Disorder, as the anxiety disorder which could be the prototype of anxiety as a memory disorder'. That this was indeed a major omission can be seen from the paper by MacDonald, Chamberlain and Long (this issue) in which they note, among other things, that 'the characteristic symptoms resulting from the exposure to

extreme trauma include persistent re-experiencing of the traumatic event' - in essence a hypermnesia. However, it should be noted that phenelzine appears more effective than imipramine in treating PTSD (Silverstone, this volume) and anxiolytic drugs do not appear to be the drugs of choice. Since phenelzine does not have 'anxiolytic' properties in our neuro-physiological tests and is highly effective in benzodiazepine-insensitive atypical depression, it is probable that PTSD should not be equated with 'anxiety proper' as this is defined here.

The subcortical neurology of anxiety

For all these reasons, it appears we can retain the view of the subcortical neurology of anxiety which we presented above. Panic (undirected escape etc) is associated primarily with the periaqueductal gray; simple phobia with the hypothalamus (directed escape) and with the amygdala (avoidance); fear proper (avoidance) with the amygdala; and anxiety (conflict) with the septo-hippocampal system.

To this simple hierarchical system must be added a number of complicating factors. Anxiety involves not only behavioural inhibition and risk analysis but also involves changes in 'arousal'. For example, a stimulus paired with shock can be used to increase the startle response of a rat to loud noise. Much elegant work by Davis (see 1992) has shown that this aspect of anxiety is handled by the amygdala and that it is in the amygdala that anxiolytic drugs act to reduce fear potentiated startle.

Likewise, I have talked, so far, as if the anxiolytic drugs produce their 'hippocampal' effects by acting on the hippocampus itself - and this may be true for some effects. However, there is extensive evidence that the anxiolytics act on the noradrenergic input from the locus coeruleus to the hippocampus (see McNaughton and Mason, 1980); on the serotonergic input from the raphe to the hippocampus (see Teicher, 1988); and on the supramammillary nucleus (McNaughton et al, 1995) which controls the frequency of hippocampal theta activity (Kirk and McNaughton, 1993). The septo-hippocampal system appears, then, to be the final common path for these effects of the anxiolytic drugs - but the drugs themselves act directly on many separate, but functionally related, areas of the brain.

The cortical neurology of anxiety

We have so far identified the septo-hippocampal system as a crucial structure supporting anxiety proper and as a direct or indirect site of action of both classical and novel anxiolytic drugs. However, there are many who would view human anxiety as having many highly cognitive features which are difficult to encompass within a set of brain structures which are present in all mammalia and which have identifiable homologues in vertebrates in general.

Of course, there is a sense in which the entire neocortex must be involved in anxiety. With the exception (rare even in rats) of innate anxiety provoking stimuli, most stimuli elicit anxiety because of an animal's prior experience and its evaluation of that experience. Human anxiety must therefore be different from rat anxiety in the nature and type of stimuli which can elicit it. Of course, rat anxiety differs from mouse or whale anxiety for the same reasons. But the fact that a red colour can provide a warning to us but not to the colour blind rat reflects a difference in perceptual and 'purely' cognitive equipment, not in the emotional systems to which the sensory systems are connected. For much of the neocortex, therefore, we must accept that there are differences between species (which give them a different 'view' of the world) but we would not want to conclude from this that the essential nature of anxiety differed between the species.

However, there are two areas of the neocortex where there appears to be a deeper link with anxiety: the prefrontal cortex and cingulate cortex. These areas are noteworthy in that their surgical removal can alleviate anxiety which is insensitive to anxiolytic drugs. They are also noteworthy for having strong reciprocal connections to the septo-hippocampal system. They could, then, be viewed as housing neocortical components of the hierarchical defense system which we have followed so far only to the archicortex.

Rapoport (1989) has suggested that the cingulate cortex, in interaction with the basal ganglia, is responsible for obssessive-compulsive disorder. By implication, this circuit would also be the basis for non-pathological obsessions and repetitive checking behaviour (e.g. parents checking repeatedly on their child in a dangerous situation). Although there is some disaggreement on this, it seems that at least some obsessive-compulsive behaviour could occur in the absence of anxiety and it is prevention of the safety ritual (by social or other factors) which results in the anxiety which ultimately brings the patient into the clinic. The cingulate also has direct connections to the amygdala and periaqueductal gray and so is well placed to be part of an integrated, hierarchical, defense system.

Prefrontal cortex, by contrast, is closely related to the premotor and motor cortices and can be viewed as controlling visual attention (via the frontal eye fields), working memory (via areas in the region of the principal sulcus) and related 'planning' functions. In terms of cytoarchitectonics it can be viewed as operating in parallel with cingulate cortex; it receives many inputs from the thalamus and related structures which are similar to the inputs to cingulate cortex; and it has an equivalent outflow to motor regions - but this is biased towards motor cortex in contrast to the cingulate bias towards the basal ganglia. If we follow the line of argument of this paper so far, we could speculate that whereas the cingulate deals with largely innate 'worries' (which can result in anxiety if the ritual is not fulfilled) the prefrontal cortex could deal with more learned 'worries' (where it controls aspects of planning which result in anxiety only if the goal is blocked). Since there are benzodiazepine receptors in the frontal cortex it is possible that some of the effects of the anxiolytics can be achieved here - but the effectiveness of prefrontal lesions in drug-resistant anxiety suggests that, like the cingulate, the prefrontal cortex deals mostly with aspects of anxiety (equivalent to obsessions in the cingulate case) that are above the level of what I have termed anxiety proper.

The neuropsychology of anxiety

A proper neuropsychology of anxiety should account for all psychological aspects of the subject in terms of a mapping

to all of the available neuroscientific information. We attempt this in our upcoming book (Gray and McNaughton, in preparation). Here it will be sufficient to point out the psychological consequences of the preliminary neurology described above - in what is intended to be an atheoretical fashion - and which is schematised in Figure 1.

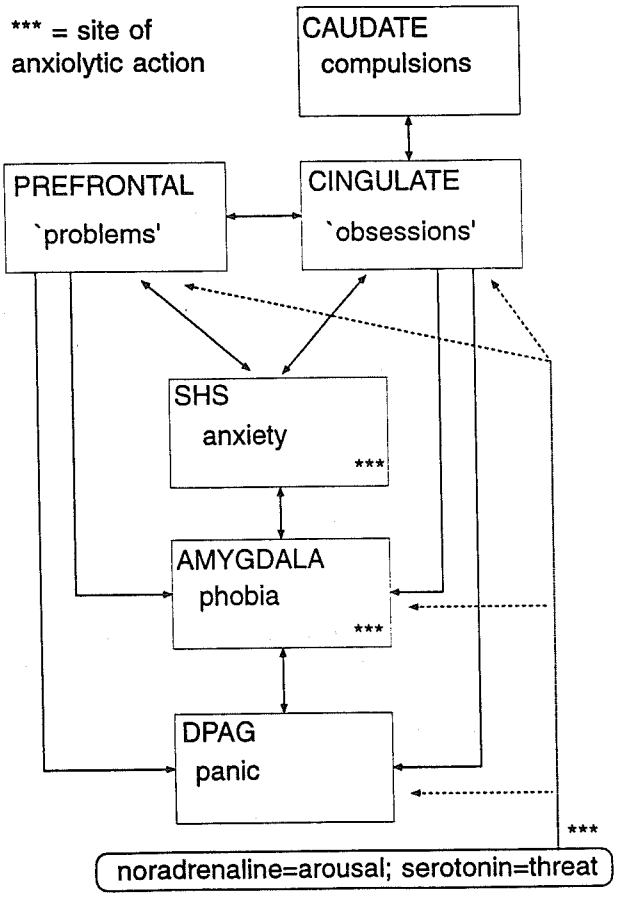
First, let us consider panic. This appears to be controlled by the periaqueductal gray (Graeff, 1994) and to be insensitive, in and of itself, to anxiolytic drugs. From this we would expect that there will be cases where a disturbance (whether biochemically or psychologically induced) of this area would result in 'pure' panic attacks. The spontaneous occurrence of such attacks (equivalent to finding oneself face to face with a predator, but for no apparent reason) would be expected to condition anxiety in exactly the same way as would a real predator. However, the randomness of the occurrence of the attacks would not allow conditioning to any specific object and so could result in the generalised avoidance of potentially dangerous places classified by DSM-IIIR as agoraphobia. Note that as the anxiety associated with agoraphobia increased this would be likely to increase the incidence of panic attacks and a potentially vicious cycle would be set up. In this context it is interesting to note that cognitive therapy of panic agoraphobia can eliminate pathological anxiety even when it does not eliminate panic attacks (Franklin 1990).

Next, let us consider simple phobia. This also is insensitive to anxiolytic drugs. Simple phobia in the clinic conflates escape tendencies and active avoidance tendencies. We view these as being controlled mainly by the hypothalamus and amygdala respectively and it may be that there is room for some new clinical subdivision here.

Next, let us consider anxiety proper. This is, by our definition, sensitive to anxiolytic drugs. The septo-hippocampal system is the primary locus of control and the final common path for anxiolytic action - but the drugs have important direct actions on a number of areas connected directly to the septo-hippocampal system (locus coeruleus; raphe nuclei; supramammillary nucleus; amygdala; prefrontal cortex). It is also the rich interconnection of the septo-hippocampal system with areas such as the amygdala, prefrontal cortex and cingulate cortex which provide the neural basis for the conditioning relationships between panic and anxiety (described above) and, for example, obsessions and anxiety (described below).

Finally, let us consider obsessive-compulsive disorder. Obsessions in and of themselves appear relatively insensitive to anxiolytic drugs and also to cognitive therapies. Here the cingulate cortex is likely to be the critical neural structure and it, or its connections to the basal ganglia, likely to be the critical site of action of drugs such as clomipramine. On the simplest view, obsessions as such could occur without anxiety (in the same way as we presumed that panic attacks could occur in the absence of anxiety) but, like panic attacks could result in psychogenic anxiety and, indeed, would virtually always be accompanied by it in people who sought clinical help. Also, like panic attacks, we can presume that the connections between the hippocampal formation and the cingulate would normally generate an increased liklihood of compulsive behaviour when there are high levels of

Figure 1
Diagram of the neural and psychological relationships between different aspects of DSM-IIIR anxiety disorder.



As defined in the article, anxiety proper (which I would tend to equate with generalised anxiety disorder) results from activity in the septo-hippocampal system (SHS) and its connections with prefrontal cortex, cingulate cortex and amygdala. Innate worries ('obsessions') are to be equated with activity in CING with compulsions resulting from consequent activity in the basal ganglia (Rapoport, 1989). Learned worries ('problems') are to be equated with activity in the PFC. Note that 'problems' and 'obsessions' are not held to give rise to anxiety unless the required goal cannot be achieved. Phobia (in the sense of avoidance of a discrete present stimulus) is to be equated with activity in the amygdala and panic is to be equated with activity in the dorsal periaqueductal gray (DPAG; Graeff, 1994). Panic can result from over activity in areas other than the DPAG or can result from activation of DPAG itself (e.g. as a result of high levels of carbon dioxide). As with obsession, panic is not equated with anxiety, but can act as an unconditioned stimulus and so give rise to anxiety via conditioning. Predisposition to anxiety disorder may well result from genetic or acquired biases in the noradrenergic and serotonergic inputs which modulate activity in all of these structures. Anxiolytic drugs act directly on these monoaminergic inputs and on the SHS and the amygdala.

anxiety and hence, again like panic, there would be the opportunity for a 'vicious cycle' of reinforcement of obsession by anxiety and vice versa. It is not clear at the present time how our analysis of frontal cortex fits with the current (DSM-IIIR) typology.

Conclusion

The (probably oversimplified) picture with which I would like to finish is of a hierarchically organised defensive system (Graeff, 1994; Le Doux, 1994) in which panic, phobia, anxiety proper, obsession and other entities can be viewed as having separate neural representations. In principle, then, pathological disturbances of any one of these centres of representation could give rise to the relevant simple symptomatology in isolation. In practice, however, the centres are not isolated. They are reciprocally interconnected in a neural network where any particular psychological state is probably best represented by a pattern of activity distributed across many centres in the network. In particular, when a patient presents in the clinic, the symptomatological picture will include not only the symptoms arising from the primary source of disturbance (e.g. spontaneous panic attacks) but also from the engagement, through experience, of other areas in the network (e.g. conditioned agoraphobia). A key point here (which does not appear to be very good engineering design, but may have adaptive value under normal ecological circumstances) is that the interaction between the centres can involve *positive* feedback. We have no guarantee, even, that what appears to be the most intense component of a set of presenting symptoms will relate to the primary source of pathology.

If this neurological picture is right, it means that we have the potential for producing a discrete typology for the 'anxiety disorders' and that this typology may well match, at the categorical level, some of the typology of DSM-IIIR. However, given the interactive neurology of the areas we have discussed, it is clear that making a differential diagnosis may be impossible if the only evidence available is the symptoms themselves. Thus, panic and anxiety may be co-resident either because 'pathological' panic has engendered 'normal' anxiety through conditioning or because 'pathological' anxiety has become sufficiently intense to elicit 'normal' panic.

It may well be, indeed, that the best basis for differential diagnosis will be behavioural tests designed to assess specific information processing operations (attributable to each of the brain areas we have discussed) in a totally non-emotive context. Thus, involvement of prefrontal cortex might be assessed by tests of working memory, involvement of cingulate cortex by tests of innate motor programmes, involvement of hippocampal formation by tests of stimulus interference in cognitive tasks and so on.

Given the advances made by modern neuroscience it is almost axiomatic that a successful theory of anxiety should be consistent with the known neurology of defense systems. I hope this paper has persuaded you that there is at least the possibility of deriving a successful psychological theory of anxiety by starting with what is known about the brain in general and about defense systems in particular.

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Continued on page 18

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