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Cognitive Dysfunction Resulting from Hippocampal Hyperactivity—A Possible Cause of Anxiety Disorder?

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McNAUGHTON, N. *Cognitive dysfunction resulting from hippocampal hyperactivity—A possible cause of anxiety disorder?* PHARMACOL BIOCHEM BEHAV **56**(4) 603–611, 1997.—Pure cognition and hence pure cognitive dysfunction might be expected to have no direct relation to any specific emotion. Changes in cognitive processing will change the assessment of stimuli and thus could change emotional responses nonspecifically. However, neurology suggests a more direct relation between at least some aspects of cognition and emotion. The limbic system in general and the hippocampus in particular have been suggested at different times to be crucial for both memory and emotion. Even recently, O'Keefe and Nadel (*The hippocampus as a cognitive map*, Oxford University Press, 1978) proposed that the hippocampus is a spatial, or cognitive, map, while Gray (*The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system*, Oxford University Press, 1982) proposed that it is central to anxiety. This apparent incongruity can be resolved by combining recent developments in the psychology of anxiety (which emphasise changed processing biases), recent extensions of Gray's theory (which bring it closer to cognitive views), and recent theories of the role of the hippocampus in memory (which see it as controlling rather than storing information). This paper proposes that at least some instances of clinical anxiety could result from hyperactivity of the septo-hippocampal system, which would produce cognitive dysfunction in the form of increased negative associations of stimuli with a consequential increase in anxiety when the stimuli are subsequently presented.

Hippocampus Theta rhythm Anxiety Anxiolytics Cognition Risk assessment Memory Behavioural inhibition

COGNITION and emotion, since they are distinct terms, might be expected to refer to quite distinct entities (indeed, in everyday speech, reason and emotion are often not only distinguished from, but contrasted with, each other). From a Darwinian point of view, however, cognition and emotion must, at least, be synergistic. Emotion, far from being something that interferes with rational action, must be something that results in adaptive responding (and hence, in a sense, rational responding), at least under phylogentically frequent circumstances (38). More significantly, perceptual and cognitive systems are, in this view, present only to provide an appropriate filter for environmental information so that it produces the appropriate "emotional" response. As a result, the cognitive equipment of an individual or species is likely to reflect the specific uses to which it can be put under its normal ecological circumstances, rather than simply maximising information processing capacity in any general way.

There is, then, reason to suppose that our cognitive equipment may be inherently emotional. That is, the "design" of our cognitive machinery may reflect the fact that it is required (in evolutionary terms) to produce "emotionally desirable" outcomes. Consistent with this general view, in this paper I will argue that generalised anxiety disorder can be the result of a purely cognitive primary dysfunction, despite the fact that it is normally characterised as an emotional disorder.

Because I am arguing for a tight, albeit consequential, link between cognition and emotion in this case, I must first argue for the making of a theoretical distinction between them. Otherwise, any relation between them could be of identity rather than consequence.

Let us first consider the case of sensory preconditioning. In this paradigm, one neutral stimulus (A) is presented consistently before a second neutral stimulus (B). No behavioural or autonomic changes are observed. However, subsequent pairing of B with a reinforcer, in the absence of A, will, when A is next presented, produce a response to A similar to that which has been conditioned to B. From this we conclude that during the A-B pairings, neural links between their representa-

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tions were strengthened, but this strengthening did not result in any specific motivational or respondent consequences (and, indeed, these consequences are wholly determined by the nature of B). In this and other learning paradigms, then, we have evidence for a change purely in the animal's cognitive structures [see (15)].

Let us next consider the case of a rat's response to cat odour. Even with no prior experience of cats, a rat will display a variety of "risk assessment" behaviours and accompanying signs of autonomic arousal when it encounters the odour of a cat [(4); see also (61)]. While there is a sense in which the cat odour must have altered the rat's cognitions and in which at least some of the changes in the rat's behaviour may depend on the presence of particular cognitions, I will take this as an example of an emotional response that is not mediated by extensive cognitive processing. Note here that, unlike the habituation of fear reactions to most novel stimuli, the response to cat odour does not appear to habituate across trials (63). More importantly, it seems likely that the observed responses would not be affected greatly by any treatment that specifically disrupts any clearly defined purely cognitive process [other than rendering the rat anosmic; although exposure to cat odour does produce significant changes in benzodiazpeine binding in the frontal cortex (26)]. Certainly we know that rage survives intact, and indeed becomes indiscriminate (and hence is known as "sham rage"), with the removal of the bulk of the forebrain [where much cognitive processing is presumed to occur; see also (58)].

Finally, let us consider the course of autonomic and hormonal reactions during avoidance conditioning. The release of corticosterone and the occurrence of defecation both increase during the initial learning of an avoidance response and then, as avoidance becomes perfect, they decrease. The changes are not due simply to the presence or absence of shock, since forced extinction (when the making of the avoidance response is blocked but no shock is delivered) also results in corticosterone release (10). Corticosterone release does not occur during learning of an appetitively reinforced task (9). Here we have cognitive processes (association of the type seen in sensory preconditioning) resulting in emotional reactions (of the type seen with cat odour) and also some evidence for higher order inference doing the same (forced extinction). In this case, then, it would be possible for a change in some purely cognitive process to produce enhanced or reduced emotional reactivity. However, note that such a change should affect a variety of reactions outside those related to the specific emotional system of interest, including many more purely cognitive tasks like sensory preconditioning requiring the same basic associative links. (Likewise, a change purely in the emotional system would not transfer to more purely cognitive tasks.)

The difficulty of separating cognition and emotion is probably more evident in the history of neuropsychology than in psychology proper. We have come some way since 1884, when William James (27) could say that

> the physiologists who, during the last few years, have been so industriously exploring the functions of the brain, have limited their attempts at explanation to its cognitive and volitional performances. Dividing the brain into sensorial and motor centres, they have found their division to be exactly parallelled by the analysis made by empirical psychology, of the perceptive and volitional parts of the mind into their simplest elements. But the *aesthetic* sphere of the mind, its longings, pleasures and pains, and its emotions have been . . . ignored.

But, except in the amassing of large amounts of detailed information, we have not come very far in sorting out the precise relations between these various entities "and yet," to continue quoting James (27), "it is even now certain that of two things concerning the emotions, one must be true. Either separate and special centres affected to them alone are their brain seat, or else they correspond to processes occurring in the motor and sensory centres, already assigned, or in others like them, not yet mapped out."

In the searches for the brain centres required by James, we have seen emotion identified with a variety of areas. It has been identified with activity in the thalamus and its interaction with the neocortex (7), which we would now view as fundamentally concerned with sensory processing and cognition. In contrast, it has also been identified with activity in the limbic system and archicortex [e.g., (56)].

Papez's (56) theory was inherently anatomical, but nonetheless encompassed a wide variety of physiological data. At its root was the distinction (maintained across a wide variety of phyla) between "the medial wall of the cerebral hemisphere [which] is connected anatomically and integrated physiologically with the hypothalamus and . . . the lateral wall [which] is similarly related to the dorsal thalamus. These fundamental relations [in lower vertebrates] are not only retained but greatly elaborated in the mammalian brain by the further development of the hippocampal formation and the gyrus cinguli in the medial wall and of the general cortex in the lateral wall of each cerebral hemisphere" [Papez (56)].

Of particular interest to our present argument is the fact that Papez essentially identified the hippocampal/cingulate elaboration with emotion and the more lateral elaborations of the cortex with what we would now see as more cognitive processes. By contrast, many modern theories see the hippocampus, at least, in more cognitive terms [e.g., the "cognitive map" of O'Keefe and Nadel (51)], although the cingulate would still be seen as a more "emotional" structure. (This separation of hippocampal formation from cingulate cortex is far from clear, and we will have reason, below, to link the posterior cingulate with the functions of the septo-hippocampal system.)

We should not be surprised that the recent view of the hippocampus as an entirely cognitive structure (albeit one with strong links to more emotional centres such as the cingulate) is totally contrary to Papez's expressed view that "the central emotive process of cortical origin may then be conceived as being built up in the hippocampal formation and as being transferred to the mammillary body and thence through the anterior thalamic nuclei to the cortex of the gyrus cinguli. The cortex of the cingular gyrus may be looked on as the receptive region for the experiencing of emotion" (56). This would not be the first time that a venerable theory has been overtaken by more recent data and, certainly, the evidence for cognitive functions of the hippocampus appears very compelling. However, subsequent to O'Keefe and Nadel's (51) presentation of "the hippocampus as a cognitive map," Gray (20) used much the same anatomical, physiological, and behavioural data to argue for the hippocampus (included within the "septo-hippocampal system") as central to "the neuropsychology of anxiety." While Gray's view is clearly not identical to that of Papez, it nonetheless suggests that the old idea of the hippocampus being directly involved in at least some emotion is far from dead.

In what follows, I will argue that, at least in the case of anxiety, emotion and cognition are linked in neural practice, even though I would not argue that they must be linked from logical necessity. Before considering this essentially data-driven argument, a caveat should be entered.

As noted by Hebb [(25), p. 236],

> traditionally, emotion is an awareness, an event in consciousness. Here, perhaps more than anywhere else in psychology, a traditional interactionism (which is animism) tends to persist. The afferent excitation is thought to produce a feeling or awareness, and *that feeling then acts on the nervous system*—it must do so, according to such ideas, for it is the feeling that makes the subject sweat or tremble or run away, and the sweat glands and the legs are controlled by nerve fibres.

In what follows, I will not only totally reject, with Hebb, the idea that emotion could involve such animism, but I will also assume that emotion does not necessarily involve conscious awareness [see, e.g., (58)], either of its presence or its true cause. (One can, for example, find oneself suddenly trembling with rage in response to some very trivial event without being conscious at that point in time of either the building up of the emotion or the prior events without which the straw would not have broken the camel's back.) Indeed, I have argued elsewhere (38) that an emotion is best viewed as a cluster of potentially independent reactions that share a common phylogenetically defined function (or, strictly, "teleonomy"). As a consequence, eliciting stimuli may provide a greater guarantee of the co-occurrence of the various components of "an emotion" than any internal coordinating system.

This somewhat spartan view of emotion (that which moves one) comes very close to making emotion a simple precursor to action—and of course it often is. In a sense, therefore, the distinction we have been considering between cognition and emotion could turn out to be no more than the conventional distinction between perception and action (alluded to by William James), but with each—perception and action—encoded at a deeper psychological and neural level. There are two points to note here. First, with an entity such as pain, for example, it is difficult to distinguish between higher order "perception" qualities and higher order "action" qualities. To say that something is painful is not only to ascribe to it a perceptual quality but also to ascribe to it an action tendency. Second, even with what appear to be logically separable classes of perception and action (even those with minimal emotional content), the brain in practice, if not of necessity, appears to conflate the machinery involved (32).

In what follows, then, I will attempt to integrate the "cognition" and "emotion" perspectives of hippocampal function by suggesting that the operations carried out by the hippocampus are in the computational sense purely cognitive but are in a practical sense inherently emotional in that the cognitive operations evolved primarily (but not solely) to control negative affective biases. If this is so, they cannot be viewed as totally emotionally neutral in the way we could view sensory preconditioning as being emotionally neutral. To achieve this integration of the different perspectives on hippocampal function, I will briefly review some critical aspects of the cognitive (essentially spatial/relational memory) and the emotional (essentially anxiety/behavioural inhibition) theories of hippocampal function and then link these with recent cognitive/memory views of anxiety disorder. This review suggests the possibility, elaborated in the final section of the paper, that at least some cases of anxiety disorder could represent a cognitive dysfunction resulting from hippocampal hyperactivity.

THE HIPPOCAMPUS AND MEMORY

There now exists a vast literature on the possible role (or roles) of the hippocampus in memory. The most comprehensive and detailed theory of that role is O'Keefe and Nadel's (51) cognitive map theory. While many specific details of that theory would no longer be accepted by most researchers in the area, it still provides the starting point for many other approaches to the subject. The key features with which there would most often be disagreement nowadays are the ideas that: a) the hippocampus deals primarily with spatial information, and b) the hippocampus represents the final repository for the information that it is involved in storing [see, e.g., (8)].

This said, one must accept that there is excellent evidence that: a) some cells in the hippocampus appear to have spatial receptive fields [see, e.g., (50)], b) damage to the hippocampus appears to produce impairments that are particularly noticeable in spatial tasks (49), and c) the amnesia that accompanies hippocampal damage in humans is most obviously a cognitive and least obviously an emotional deficit (although H. M. does not appear to experience much anxiety; J. Ogden, pers. comm.).

Many of the defects of a *purely* spatial view of the hippocampus [which is more extreme even than the original, 1978, view espoused by O'Keefe and Nadel (51)—witness their term "cognitive map" rather than spatial map] can be resolved by two manoeuvres: a) an expansion of the presumed nature of the cognitive dysfunction involved, and b) a translation of the site of final information storage to the neocortex (and possibly subcortical areas as well).

Both these manoeuvres are exemplified in Cohen and Eichenbaum's (8) theory in which the hippocampus is held to be crucial for the processing of relational information. In essence, this extends O'Keefe and Nadel's (51) theory by casting spatial stimuli as a subclass of stimuli in which the relation between stimulus elements is crucial. Their theory also holds that the hippocampus is necessary for the formation of the "relation" involved, but that the neocortex is the final site of the resultant construct.

For the present purposes, it will not be necessary to go into these theories (or a number of other less well developed recent theories) in detail. The crucial point is that they categorise hippocampal function in an almost purely "cognitive" fashion and that they account for large amounts of the single cell and lesion data. However, there are some areas of data that they do not readily explain and that the theorists implicitly or even explicitly exclude from consideration.

For example, Eichenbaum, Otto and Cohen (16) stated that they "will not consider the large body of literature on the effects of hippocampal system damage on behaviors that are only indirectly related to learning and memory, including studies on orientation, distraction, exploration, motor patterns, operant schedules, emotion, and species specific behaviours." While to some extent they may be right that "changes in these behaviours after hippocampal system damage are either a consequence of amnesia or an indirect result of disconnections of the limbic system that have non-mnemonic as well as mnemonic effects," their strategy clearly leaves open the possibility of the reverse: that the apparently mnemonic effects of hippocampal damage are a consequence of some more general non-mnemonic role of this structure.

We [Gray and McNaughton, in prep. (22)] are currently updating Gray's (20) original theory to provide a detailed exposition of such an alternative view. However, the gist of our argument against the general class of view that the hippocampus is required specifically for the formation of memories is as follows. First, "memory" theories generally ignore the massive subcortical input and output of the hippocampal formation. Second, they ignore the selective effects of hippocampal lesions on learning to inhibit responding (e.g., extinction of running), in contrast to sparing of acquisition of the same

responses. Third, they do not account for the fact that amnesics often show intrusion errors (responses that would have been correct on a previous trial), suggesting that, in amnesics, information is stored, but not correctly retrieved. These and other data are consistent with the idea that the hippocampus is important for, e.g., relational processing, but suggest that its function is to suppress the formation of, say, incorrect relations rather than to promote the formation of correct ones. An important feature of this inversion of the conventional memorial view is that it allows translation to nonmemorial and, indeed, innate tasks, where the hippocampus would be held to inhibit the production of inappropriate alternatives.

Let us see how this inhibitory view of the hippocampus fares in the context of the view that relational processing is a key to sensitivity to hippocampal lesions—a view which seems well justified by Eichenbaum et al. Note first that Eichenbaum et al. see neocortical association areas as "the final repositories of long-term memory". On current views of cell assemblies, this implies that all the connections required for multimodal relational processing are already present between areas of the neocortex before the hippocampus is called into play. We can also assume that the plasticity rules of the network are such that simple associations can be made without the hippocampus. Given this combination of connections and plasticity, why is the hippocampus needed at all?

A network tuned to make simple associations on the basis of a simple Hebbian learning rule would be likely to make innumerable partial, incorrect associations when required to make relational associations. That is, faced with a problem which requires one specific relational solution, the network would be likely to produce, albeit in some cases at lower strength, additional incorrect solutions—akin to the case of stimulus saturation [e.g. B. McNaughton and Morris, 1987 (36)]. An essentially inhibitory role of the hippocampus, which increased the signal-to-noise ratio in the cortex, would solve this problem. The hippocampus would interact with the neocortex to inhibit the inappropriate, conflicting alternatives (in this case stimulus alternatives) [McNaughton (39)].

In this view, then, the hippocampus is necessary for the formation of certain types of memories because it interacts recursively with the neocortex [see also (48)], and also subcortical areas [see (57)], at times when there is major conflict between alternatives (as is generally the case for relational tasks). At all times, however, the critical information would be encoded and stored outside the hippocampus. Because of its recursive interaction with active extrahippocampal areas, cell firing patterns within the hippocampus would reflect concurrent cortical activity to a large extent, but in a modified form, reflecting the role of the hippocampus in selectively and actively suppressing some of that extrahippocampal activity. In a sense, the hippocampus would be producing a form of dynamic lateral inhibition.

This position is argued in considerable detail elsewhere (20,22), but its precise truth is not important for the present argument. All that is required, here, is acceptance of the possibility that the hippocampus may have an essentially unitary function that goes beyond the bounds of purely memorial processing, and the possibility that this unitary function may be in some sense or another inhibitory (especially with respect to the formation of new cortical connections).

THE HIPPOCAMPUS AND ANXIETY

Gray's (20) theory of the functions of the septo-hippocampal system places the hippocampus at the core of a system of interconnected structures that form his "Behavioural Inhibition System" (BIS). The key features of this system are that it responds to signals of novelty, punishment, and nonreward and produces a variety of outputs including inhibition of prepotent behaviour, increased attention, and increased arousal. In its original form, the theory was heavily based on learning experiments but, in line with our analysis of the innate effects of cat odour, it is noteworthy that novel stimuli and cat odour produce very similar effects on benzodiazepine receptor binding in the hippocampus, although they produce different patterns in prefrontal cortex (26).

The cornerstones of the theory are the fact that anxiolytic drugs produce behavioural effects that are remarkably similar to those of septo-hippocampal system lesions and the fact that anxiolytic drugs impair the control of theta activity. (Theta activity is a characteristic phase-locked synchronisation of firing of the cells of the hippocampus and of related structures such as the entorhinal and posterior cingulate cortex; these latter structures are included within our definition of the septo-hippocampal system.) These two facts suggest that the anxiolytics produce their behavioural effects by impairing the control of theta activity.

Since the publication of the 1982 version of Gray's theory (20), considerable data have accumulated that, on the one hand, greatly strengthen his general position, while, on the other hand, requiring modifications that move it closer to the memorial theories.

The theory has been greatly strengthened by recent data obtained with novel anxiolytic drugs such as buspirone, which do not share any of the side effects of classical anxiolytics (e.g., the benzodiazepines). The novel anxiolytics produce (at least within a narrow dose range) many of the behavioural effects of hippocampal lesions [e.g., (52–55,68); see (24) for a review]. It is also striking that they reproduce both of the two physiologically and neurochemically distinct actions on the control of theta activity that are characteristic of classical anxiolytic drugs (40,41,46,47,64–69). Such differences as there are between buspirone and the classical anxiolytics (particularly the narrow effective dose range of the former) appear likely to be due to an antagonistic action of corticosterone (45), which is released by buspirone but suppressed by classical anxiolytics. There are also indications that these differences disappear with repeated administration of the drugs (68).

In this context, it is noteworthy that the two tests used to assess the effects of anxiolytic drugs on the control of hippocampal theta activity are virtually the only tests in the literature on screening of anxiolytics that show clear positive results with all the classical and novel anxiolytics that have been tested (including anxiolytic antidepressants such as imipramine). They are also among the few tests of any kind to show linear dose–response curves with buspirone.

The same novel anxiolytic, buspirone, that provides this strong support of the theory (in the sense that the theory can be said to have predicted its behavioural and neural effects from its clinical action before the latter was known) also provides data that bring the theory closer to the memorial views of hippocampal function.

As noted in the previous section, the spatial view of hippocampal function is one of the oldest and most robust. Certainly, whatever the detailed merits of the position taken by O'Keefe and Nadel in 1978 (51), an interference with specifically spatial performance in tasks such as the Morris water maze is highly characteristic of disturbances of hippocampal function (49). It is of peculiar significance, therefore, that not only classical anxiolytics (43) but also buspirone (44) impair spatial navigation in the water maze, and do so most clearly in measures of spatial localization while leaving intact what appears to be taxon learning [see (51)].

The effects of anxiolytics (or indeed hippocampal lesions) on performance in the water maze cannot be accounted for simply as a loss of inhibitory learning—since the task is an example of active rather than passive avoidance [see (21) for the importance of this distinction]. There are, however, at least two other possibilities. First, hippocampal dysfunction could result in a failure to inhibit the many competing tendencies (e.g., swimming in circles) that are available to, and displayed by, animals during the early part of acquisition. Second, following straightforwardly from the theory of Eichenbaum et al. (16), the relational nature of the task would require the inhibition of responding to all but a subset of the available configurations of stimuli. These possibilities are not mutually exclusive, and it is interesting here that we have recently shown that systemic administration of chlordiazepoxide, an anxiolytic benzodiazepine, reduces theta frequency in the water maze and impairs learning both early and later in acquisition, whereas its injection into the supramammillary nucleus (28,29) reduces theta frequency more specifically and to a more modest extent (42) and impairs spatial navigation only later in acquisition (Pan and McNaughton, in prep.). Injection into the supramammillary nucleus would not be expected to produce any of the systemic side effects of the drug, nor, importantly, is it likely to reproduce the effects of systemic administration on the septal control of theta activity (41), which can be attributed to an action on the dorsal ascending noradrenergic bundle (23). It could well, therefore, be dissecting out just one aspect of the hippocampal control of learning in this situation.

We come now to the nub of the argument. We have available a group of drugs whose only known common clinical action is to ameliorate generalized anxiety disorder (e.g., buspirone does not affect panic disorder). This group produces, as a common action, a deficit in one of the most cognitive and memorial tests of hippocampal function. Admittedly, the animal in the water maze must feel some negative reaction to the water or it would not climb out. However, rats do not struggle or squeal when being placed in the water, they can float at will, and, as was mentioned before, the test is one of active rather than passive avoidance. Active avoidance, as such, is not impaired by anxiolytic drugs or hippocampal lesions. The role of emotion, per se, in the effects of the drugs on spatial navigation is, therefore, very difficult to discern. It is simplest to conclude that the drugs are acting on an essentially cognitive rather than emotional process, but that this cognitive process is one that is fundamental to the generation of anxiety and is, in that sense, not cognitively neutral.

MEMORY AND ANXIETY

We have come now perilously close to concluding that anxiety is a cognitive rather than emotional state. But we should remind ourselves here that the much clearer distinction between perception and action nonetheless allows for some overlap in the brain processes involved in each (32). That this may also be the case with cognition and emotion in anxiety is supported by recent developments in the cognitive analysis of anxiety (and, by implication, anxiety disorder) provided separately by Eysenck (17) and by Mathews and MacLeod (33), essentially following from the earlier view of Beck, (see 33) which will be considered in the next section.

This support is somewhat ironic since, in evaluating Gray's (20) theory, Eysenck (17) concluded that

> while [Gray's] theory may provide an excellent model of anxiety, it is not altogether clear that it is an adequate account for individual differences in trait anxiety at the human level. Gray may well be right that there are important similarities between rat and man in terms of the brain structures which mediate anxiety, but it is much less likely that the cognitive processes associated with anxiety are the same in the two species. This point was made rather well by Hallam: "Even if the layman or clinician were to accept that perceiving events as, say, signals of punishment or non-reward called forth biological responses that we have in common with other species, they might still argue that the cause of the complaints of anxiety was in perceiving events in this way, and not in possessing the biological mechanism of response."

In effect, Eysenck has accused Gray of not being cognitive enough and yet, in its more novel incarnation, presented above, the problem is that the theory has almost been forced into being too cognitive!

Before we move on to the cognitive analysis of anxiety per se, we should deal with two basic issues relating to Hallam's comments cited by Eysenck (17).

First is the issue of the "biological responses" involved in anxiety. If this term is taken to mean "innate responses," it cannot be held to refer to Gray's theory [which is, in the 1982 version (20), fundamentally based on conditioning experiments]. It must, then, be taken to imply a distinction between biological responses and perception or cognition. But this is, surely, a recrudescence of the "animism," which, with Hebb, I rejected in the introduction to this paper. Of course, human frontal cortex is larger than rat frontal cortex (as is neocortex in general), but there is no evidence that its basic organization and subdivisions are substantially different. Likewise, there is no good reason to suppose that human cingulate cortex is functionally divergent from rat cingulate cortex. For both frontal and cingulate cortex (and particularly, as noted above, posterior cingulate), we should expect a contribution to anxiety that is no different in basic kind in rat and human. Of course, rats will not respond identically to humans (e.g., they are colour blind) but, in this sense, no two individual humans will respond identically to each other either.

Second is the issue of adequate stimuli for anxiety and hence for the activation of the behavioural inhibition system. Gray in his 1982 preface (20) warned that "it is not claimed that the septo-hippocampal system is concerned only with anxiety, nor that anxiety depends solely on that system." He defined the BIS in terms of activation by novel stimuli, innate fear stimuli, and predictors of punishment and nonreward. Recent work by the Blanchards [e.g., (2–5)] and by a number of workers analysing the amygdala [see, e.g., (14,30)] has suggested some refinement and clarification of this position.

The Blanchards [e.g., (2–5)] carried out an extensive series of ethoexperimental and ethopharmacological experiments that suggest a categorical distinction between defensive responses elicited by the presence of a predator and those elicited by the risk of a predator. We should note particularly here that: a) it is only the risk-related behaviours that are affected by anxiolytic drugs; b) both inhibition of prepotent behaviour and elicitation of active risk assessment behaviour are changed by the drugs; and c) while both increases and decreases in risk assessment behaviour can be observed, in all cases the changes produced by the drugs correspond to a decrease in the perception of risk (potential threat). The Blanchards' data can be made consistent with previous data on the BIS by noting that the drugs are active only on those behaviours which are crucial for the entry of the animal into a threatening situation as opposed to its exit from a threatening situation. This is particularly obvious in the effects of chlordiazepoxide on rats exposed to cat odour (62), where it was found that the drug reduced the effect of cat odour on ap-

proach to a cloth impregnated with the odour but did not reduce avoidance of the odour in terms of time spent in shelter. The Blanchards' data are, in one sense, therefore, a special case of the more general involvement of the BIS in anxiety. However, in another sense, the reverse is the case. Each of the stimulus categories originally classified by Gray (20), ad hoc, as sources of input to the BIS is a subclass of the more general case of situations in which the animal must resolve a conflict between approach to and avoidance of an aversive situation. This single rubric encompasses especially the class of innate fear stimuli (or better, given the Blanchards' terminology, innate anxiety stimuli), which had no strong theoretical basis in Gray's conditioning-oriented analysis.

Work on the amygdala [a structure ignored in Gray's 1982 (20) theory] makes it very likely that it is the seat of the attentional and activational, as opposed to cognitive or inhibitory, aspects of the BIS and that anxiolytic drugs, including buspirone, act directly on the amygdala [e.g., (14)] in addition to their common action on the septo-hippocampal system.

From all of the above, it seems likely that the contribution of the hippocampus to the BIS is to detect conflict between alternative responses (specifically between approach and avoidance in situations in which the animal believes there is a potential threat), assess the consequences (engaging in risk assessment in response to potential threat), and, where necessary, resolve the conflict by increasing the salience of negative associations (hence often leading to avoidance in defensive situations). An important point here is that, in relation to the responses to innate cat odour considered above, the most marked effects appear to be on subsequent responding as opposed to direct responses (61). All of the above description could also apply to the operation of the hippocampus in relatively nonthreatening situations (e.g., the water maze), where conflict between alternative responses is engendered by stimulus complexity or interference rather than opposed motivations. In addition, however, and probably only in the case of threatening situations, the hippocampus would interact with the amygdala (with which it has reciprocal connections that would allow amplification of an existing amygdaloid activation) to produce the attentional and autonomic aspects of anxiety.

A corollary of this argument is that anxiolytic drugs would be expected to have detectable effects on human learning and memory (paralleling their effects in animals). Considerable caution must be exercised here. It is true that "amnesic effects were recognised early on by anaesthetists using benzodiazepines as premedicants [and] . . . that research in this field has mushroomed in volume. . . . [But] in view of the fact that the amnesic effects of benzodiazepines were reported in the 1960s in the anaesthesiology literature, it is puzzling why so little is known in the 1990s about the cognitive effects of benzodiazepines on people who have taken these drugs daily . . . over a period of months or years" [(11), pp. 1, 6]. The answer must be that the effects on memory of chronic administration of the drugs at conventional anxiolytic doses are relatively small (as indeed they are in animal tests), although some effects on episodic memory have been reported [see (11)]. Certainly, the results obtained by anaesthetists cannot be taken at face value, since benzodiazepines, at least, show quite distinct state-dependent and "truly anxiolytic" actions (37), and it is only the latter that are relevant to the present theoretical position.

Nonetheless, there is some evidence from brief tasks (which would not suffer from the state-dependency problem) that benzodiazepines "impair performance on explicit memory tasks but . . . have no effect on implicit memory tasks" [(1), p. 267]. This is the pattern one would predict if their action were hippocampally mediated [see also (6)], and this type of data has led to the hypothesis that "the benzodiazepines might simulate, or model, the form of memory dysfunction . . . that is expressed in the typical amnesic patient. . . . [Further,] recent studies suggest that the sedative and memory impairing effects of the benzodiazepines can be dissociated from one another" (13). Nonetheless, given the many side effects of the drugs and the acute nature of administration (which would not allow the side effects to develop tolerance), we should not put too much weight on these apparently positive results. This is especially true since, with long-term high-dose administration, the effects of diazepam on memory and anxiety can apparently show some dissociation (59).

Given the potential for false positive reporting of amnestic effects of benzodiazepines, reports of differentially lesser effects on memory with buspirone compared with diazepam [e.g., (31)] could well represent false negatives. This is particularly true in the animal literature, since acute administration of buspirone usually shows an inverted-U dose–response curve with a very narrow effective range (although the water maze is an exception to this). Indeed, the animal data suggest that benzodiazepines have side effects that inflate their apparent effectiveness and that buspirone has side effects that antagonize its effectiveness. Luckily, in both cases, these side effects appear to show tolerance after several weeks of administration, and then the two types of drug show more similar effects (67). A comparison of the amnestic effects of benzodiazepines and azapirones in humans after several weeks of administration of modest (anxiolytic) doses has not to my knowledge been published. However, a study reporting significant memory impairment with buspirone did use repeated adminstration of a low dose of the drug (35), whereas a single adminstration of the same dose did not have an effect (34).

In all this, it should be remembered that anxiolytics would not be expected to produce total hippocampal dysfunction. They alter the control of, but do not eliminate, theta rhythm, and even elimination of theta rhythm does not produce total hippocampal dysfunction. What we are looking for, therefore, in both anxiolytic action and in the predisposition to anxiety is a modest alteration in cognitive processing not total amnesia.

COGNITION AND ANXIETY

We can now turn to consideration of recent developments in the study of cognitive aspects of anxiety. These are quite complex but, as with the treatment of hippocampal theories above, only the general thrust is important for the present paper. In a nutshell, it seems likely that clinical anxiety can result from cognitive dysfunction in the form of distortions of the assessment of risk.

Thus, Mathews and MacLeod (33), in their review of cognitive approaches to emotional disorders, concluded that

> early automatic (pre-attentive) analysis of emotional information is relatively global, and perhaps confined to classifying a stimulus as potentially threatening, but that subsequent processing becomes increasingly selective, favoring information that matches current concerns. . . . Anxious mood (or stressful events) leads high, but not low, trait anxious subjects to selectively encode threatening information. . . . These observations are consistent with the possibility that individual differences in selective encoding represent the cognitive substrate of vulnerability to emotional disorder.

This view is not far from the suggestion that those prone to anxiety have a relatively high negative bias in their assessment of risk. However, the selectivity of processing has a

particularly interesting feature from the present point of view. Eysenck (17) noted that many studies of responses to threatening and nonthreatening stimuli, presented separately, show no differences between these classes of stimuli in recognition thresholds between trait anxious and trait nonanxious subjects. However, there is better evidence for

> a selective mechanism which is used when at least one threatening and one neutral stimulus are presented concurrently. . . . Those high in trait anxiety will allocate processing resources to the threatening stimulus rather than to the neutral one. . . . The selective mechanism cannot be used in situations . . . in which only one stimulus is presented at a time. . . . [Similarly,] when ambiguous stimuli are presented which can be interpreted in either a threatening or a neutral fashion, those high in trait anxiety typically produce a greater number of threatening interpretations than those low in trait anxiety for for [Eysenck (17)].

We should note in particular here that the cognitive differences being discussed are related to trait anxiety. Likewise,

> patients who have recovered from generalized anxiety disorder and normals high in trait anxiety both exhibit greater susceptibility to distraction with threat-related distractors than with non-threatening or neutral distractors. If high trait anxiety can be regarded as predisposing to generalized anxiety disorder, then these findings provide reasonable evidence for the notion that sensitivity to threat distraction forms part of a cognitive vulnerability factor for generalized anxiety disorder. The notion that sensitivity to threat distraction depends primarily on long-lasting structural effects within the cognitive system rather than being a function of the current level of experienced or state anxiety is strengthened by the additional finding that the effects of threat distraction were unaffected by the Ss' level of state anxiety [Eysenck and Byrne (18)].

In contrast to this trait-based difference in selective processing under conditions of conflict, increased inhibition of responding when challenged with single emotional stimuli (whether of positive or negative valence) appears to be state-based and is sensitive to treatment with selective serotonin uptake inhibitors (60).

HIPPOCAMPAL HYPERACTIVITY, COGNITIVE DYSFUNCTION, AND ANXIETY DISORDER: A SPECULATION

The various strands of the argument can now be drawn together into a thread that will support at least some speculation on the role of the hippocampus in anxiety and perhaps in individual proneness to anxiety.

The evidence very strongly suggests that anxiolytic drugs act to impair hippocampal function and that, *with respect to cognitive and inhibitory aspects* of anxiety, the hippocampus is their main final common path of action. This suggestion can be linked with the role of the hippocampus in amnesia via the idea that the hippocampus acts to resolve conflicts between stimuli and/or responses by amplifying the weight of negative associations. In the memory case, such negative associations represent simply the past history of reinforcement contingencies, but in approach–avoidance conflicts the negative associations represent innate or learned warnings of threat. Hippocampal hypofunction then leads to "amnesia" because of a failure to suppress inappropriate alternative responses as a result of insufficient negative bias and a consequent failure to extract the correct item from the "pandemonium" of retrievable items. (In this sense, hippocampally damaged subjects could perhaps be more correctly termed "hypermnesic" than "amnesic.") Hippocampal hyperfunction would usually lead to anxiety because of a greatly increased perception of the level of threat in situations involving conflicting stimuli or response alternatives and an increased suppression of positive actions and cognitions (not, as in the other current theories, an increased production of negative actions or cognitions).

An important point at which this largely hippocampal view of anxiety disorder departs from the conventional cognitive views is that it suggests the possibility that anxiety disorder, in at least some cases, could reflect a dysfunction that is primarily cognitive and only secondarily emotional. That is, hippocampal hyperfunction could produce a general tendency to resolve conflicts in terms of high negative bias, even in memory tasks that have no obvious threat component. If this is true, then proneness to anxiety could be assessed with analogues of animal tests such as delayed matching to sample (which minimises threat and would, therefore, not be contaminated by state anxiety). In these cases, then, anxiety proper would be seen as a secondary consequence in a normal amygdala of excessive input from a dysfunctional hippocampus interacting with the presence of mild warnings of threat in the environment.

Another possibility is that it is the circuit interconnecting the hippocampus and amygdala that could be the site of dysfunction. In this case, the disorder could be classified as both cognitive (on the hippocampal side) and emotional (on the amygdala side). However, given the very close parallels in the action of buspirone and classical anxiolytic drugs on the control of hippocampal theta rhythm, despite the fact that they have no known common direct site of action, it seems very unlikely that the dysfunction in anxiety disorder would be purely amygdaloid. On the present evidence of hippocampal and amygdaloid function, therefore, it seems unlikely that anxiety disorder will prove to be "purely emotional," although there could well be more or less cognitive (primarily hippocampal in origin) and more or less emotional (primarily amygdaloid in origin) subtypes. [We should also allow for a form of generalized anxiety disorder that depends more on prefrontal cortical dysfunction and that would be relatively insensitive to anxiolytic drugs, but this is beyond the scope of the present paper [Gray and McNaughton, in prep. (22)].]

A final link between memory and anxiety is furnished by the fact that, in anxious patients, both benzodiazepines and buspirone take a large number of days to produce their specific anxiety-reducing effects [but see Fig. 3 of (12)]. Given the immediate effects of the drugs on hippocampal function and on the acquisition of inhibitory learning, we can interpet the delay in therapeutic effect as extinction (or forgetting) resulting from the removal by the drugs of what is, in effect, a reinforcement mechanism. This separation of shorter and longer term effects could also underlie the apparent retention of processing bias even when acute doses of benzodiazepine reduce retention of information generally (19).

The truth or otherwise of these speculations will require considerable further data to determine. The main conclusion of this paper is that it should be fruitful (despite the doubts of those studying human cognition) to test human anxiety cases with tests of the type that are normally ideal for displaying hippocampally mediated cognitive dysfunction across a range of other animal species.

REFERENCES

1. Bishop, K. I.; Curran, H. V.: Psychopharmacological analysis of implicit and explicit memory: A study with lorazepam and the benzodiazepine antagonist flumazenil. Psychopharmacology 121: 267–278; 1995.
2. Blanchard, D. C.; Blanchard, R. J.: Effects of ethanol, benzodiazepines and serotonin compounds on ethopharmacological models of anxiety. In: McNaughton, N.; Andrews, G., eds. Anxiety. Dunedin, New Zealand: University of Otago Press; 1990.
3. Blanchard, D. C.; Blanchard, R. J.; Rodgers, R. J.: Risk assessment and animal models of anxiety. In: Olovier, B.; Mos, J.; Slangen, J. L., eds. Animal models in psychopharmacology. 1991:117–134.
4. Blanchard, R. J.; Blanchard, D. C.: Anti-predator defense as models of animal fear and anxiety. In: Brain, P. F.; Parmigiani, S.; Blanchard, R. J.; Mainardi, D., eds. Fear and defence. Chur, Switzerland: Harwood Academic Publishers; 1990:89–108.
5. Blanchard, R. J.; Yudko, E. B.; Rodgers, R. J.; Blanchard, D. C.: Defense system psychopharmacology: An ethological approach to the pharmacology of fear and anxiety. Behav. Brain Res. 58: 155–165; 1993.
6. Brown, J.; Brown, M. W.: The effects of repeating a recognition test in lorazepam-induced amnesia: Evidence for impaired contextual memory as a cause of amnesia. Q. J. Exp. Psychol. 42A:279–290; 1990.
7. Cannon, W. B.: The James–Lange theory of emotion. Am. J. Psychol. 39:115–124; 1927.
8. Cohen, N. J.; Eichenbaum, H.: Memory, amnesia and the hippocampal system. Cambridge, MA: MIT Press; 1993.
9. Coover, G. D.; Goldman, L.; Levine, S.: Plasma corticosteone increases produced by extinction of operant behaviour in rats. Physiol. Behav. 6:261–263; 1971.
10. Coover, G. D.; Ursin, H.; Levine, S.: Plasma corticosterone levels during active avoidance learning in rats. J. Comp. Physiol. Psychol. 82:170–174; 1973.
11. Curran, H. V.: Benzodiazepines, memory and mood: A review. Psychopharmacology 105:1–8; 1991.
12. Cutler, N. R.; Sramek, J. J.; Hesselink, J. M. K.; Krol, A.; Roeschen, J.; Rickels, K.; Schweizer, E.: A double-blind, placebo-controlled study comparing the efficacy and safety of ipsapirone versus lorazepam in patients with generalized anxiety disorder: A prospective multicenter trial. J. Clin. Psychopharmacol. 13:429–437; 1993.
13. Danion, J. M.; Weingartner, H.; File, S. E.; Jaffard, R.; Sunderland, T.; Tulving, E.; Warburton, D. M.: Pharmacology of human memory and cognition: Illustrations from the effects of benzodiazepines and cholinergic drugs. J. Psychopharmacol. 7:371–377; 1993.
14. Davis, M.: The role of the amygdala in fear conditioning. In: Aggleton, J. P., ed.: The amygdala. New York: Wiley-Liss; 1992.
15. Dickinson, A.: Contemporary animal learning theory. Cambridge, UK: Cambridge University Press; 1980.
16. Eichenbaum, H.; Otto, T.; Cohen, N. J.: Two functional components of the hippocampal memory system. Behav. Brain Sci. 17: 449–518; 1994.
17. Eysenck, M. W.: The nature of anxiety. In: Gale, A.; Eysenck, M. W., eds. Handbook of individual differences: Biological perspectives. New York: John Wiley & Sons; 1992:157–178.
18. Eysenck, M. W.; Byrne, A.: Anxiety and suceptibility to distraction. Pers. Individ. Differ. 13:793–798; 1992.
19. File, S. E.; Goodall, E. M.; Fluck, E. J.; Sanders, F. L.; Murray, A.; Skelly, A. M.; Joyce, E. M.: Contrasting effects of midazolam and nitrous oxide on memory and cognitive bias in dentally phobic patients. Hum. Psychopharmacol. 8:195–202; 1993.
20. Gray, J. A.: The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. Oxford, UK: Oxford University Press; 1982.
21. Gray, J. A.; McNaughton, N.: Comparison between the behavioural effects of septal and hippocampal lesions: A review. Neurosci. Biobehav. Rev. 7:119–188; 1983.
22. Gray, J. A.; McNaughton, N.: The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system, 2nd ed. Oxford, UK: Oxford University Press; in prep.
23. Gray, J. A.; McNaughton, N.; James, D. T. D.; Kelly, P.: Effect of minor tranquillisers on hippocampal theta rhythm mimicked by depletion of forebrain noradrenaline. Nature 258:424–425; 1975.
24. Griebel, G.: 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: More than 30 years of research. Pharmacol. Ther. 65:319–395; 1995.
25. Hebb, D. O.: The organization of behaviour. New York: John Wiley & Sons; 1949.
26. Hogg, S.; File, S. E.: Regional differences in rat benzodiazepine binding in response to novelty and cat odor. Neuropharmacology 33:865–868; 1994.
27. James, W.: What is an emotion? Mind 9:188–205; 1884. [Reprinted in Arnold, M., ed.: The nature of emotion. New York: Penguin; 1968.]
28. Kirk, I. J.; McNaughton, N.: Supramammillary cell firing and hippocampal rhythmical slow activity. NeuroReport 2:723–725; 1991.
29. Kirk, I.; McNaughton, N.: Mapping of differential effects of procaine on frequency and amplitude of reticularly-elicited hippocampal rhythmical slow activity. Hippocampus 3:517–526; 1993.
30. Le Doux, J.: Emotion and the amygdala. In: Aggleton, J. P., ed. The amygdala. New York: Wiley-Liss; pp. 339–352; 1992.
31. Lucki, I.; Rickels, K.; Giesecke, M. A.; Geller, A.: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. Br. J. Clin. Pharmacol. 23:207–211; 1987.
32. MacKay, D.: The organization of perception and action. Berlin: Springer-Verlag; 1987.
33. Mathews, A.; MacLeod, C.: Cognitive approaches to emotion and emotional disorders. Annu. Rev. Psychol. 45:25–30; 1994.
34. McKay, G.; Alford, C.; Bhatti, J. Z.; Curran, S.; Hindmarch, I.: Effects of acute doses of buspirone and clobazam on cognitive function and psychomotor performance. Med. Sci. Res. 17:301–302; 1989.
35. McKay, G.; Alford, C.; Bhatti, J. Z.; Curran, S.; Hindmarch, I.: Repeated dose effects of buspirone and clobazam on cognitive and psychomotor performance. Med. Sci. Res. 17:325–326; 1989.
36. McNaughton, B. L.; Morris, R. G. M.: Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci. 10:408–415; 1987.
37. McNaughton, N.: Chlordiazepoxide and successive discrimination: Different effects on acquisition and performance. Pharmacol. Biochem. Behav. 23:487–494; 1985.
38. McNaughton, N.: Biology and emotion. Cambridge, UK: Cambridge University Press; 1989.
39. McNaughton, N.: The hippocampus: Relational processor or antiprocessor? Behav. Brain Sci. 17:487–488; 1994.
40. McNaughton, N.; Coop, C. F.: Neurochemically dissimilar anxiolytic drugs have common effects on hippocampal rhythmic slow activity. Neuropharmacology 30:855–863; 1991.
41. McNaughton, N.; James, D. T. D.; Stewart, J.; Gray, J. A.; Valero, I.; Drewnowski, A.: Septal driving of hippocampal theta rhythm as a function of frequency in the male rat: Drug effects. Neuroscience 2:1019–1027; 1977.
42. McNaughton, N.; Logan, B.; Panickar, K. S.; Kirk, I.; Pan, W.-X.; Brown, N. T.; Heenan, A.: The contribution of synapses in the medial supramammillary nucleus to the frequency of hippocampal theta rhythm in freely-moving rats. Hippocampus 5:534–545; 1995.
43. McNaughton, N.; Morris, R. G. M.: Chlordiazepoxide, an anxiolytic benzodiazepine, impairs place navigation in rats. Behav. Brain Res. 24:39–46; 1987.
44. McNaughton, N.; Morris, R. G. M.: Buspirone produces a dose-related impairment in spatial navigation. Pharmacol. Biochem. Behav. 43:167–171; 1992.
45. McNaughton, N.; Panickar, K. S.; Logan, B.: The pituitary–adrenal axis and the different behavioural effects of buspirone and chlordiazepoxide. Pharmacol. Biochem. Behav. 54:51–56; 1996.
46. McNaughton, N.; Richardson, J.; Gore, C.: Hippocampal slow waves generated by reticular stimulation: Common effects of anxiolytic drugs. Neuroscience 19:899–903; 1986.
47. McNaughton, N.; Sedgwick, E. M.: Reticular stimulation and hip-

pocampal theta rhythm in rats: Effects of drugs. Neuroscience 3:629–632; 1978.
48. Miller, R.: Cortico-hippocampal interplay and the representation of contexts in the brain. Berlin: Springer-Verlag; 1991.
49. Morris, R. G. M.; Garrud, P.; Rawlins, J. N. P.; O'Keefe, J.: Place navigation impaired in rats with hippocampal lesions. Nature 297:681–683; 1982.
50. O'Keefe, J.; Burgess, N.: Geometric determinants of the place fields of hippocampal neurons. Nature 381:425–428; 1996.
51. O'Keefe, J.; Nadel, L.: The hippocampus as a cognitive map. Oxford: Oxford University Press; 1978.
52. Panickar, K. M.; McNaughton, N.: Dose–response analysis of the effects of buspirone on rearing in rats. J. Psychopharmacol. 5:72–76; 1991.
53. Panickar, K. M.; McNaughton, N.: Effects of buspirone on fixed interval responding in rats. Psychopharmacology 5:410–417; 1991.
54. Panickar, K. M.; McNaughton, N.: Comparison of the effects of buspirone and chlordiazepoxide on differential reinforcement of low rates of response. Eur. J. Pharmacol. 210:307–313; 1991.
55. Panickar, K. M.; McNaughton, N.: Comparison of the effects of buspirone and chlordiazepoxide on successive discrimination in rats. Pharmacol. Biochem. Behav. 39:275–278; 1991.
56. Papez, J. W.: A proposed mechanism of emotion. Arch. Neurol. Psychiatry 38:725–743; 1937.
57. Risold, P. Y.; Swanson, L. W.: Structural evidence for functional domains in the rat hippocampus. Science 272:1484–1486; 1996.
58. Stoerig, P.: Varieties of vision: From blind responses to conscious recognition. Trends Neurosci. 19:401–406; 1996.
59. Wees, H. G.; Steinberg, R.; Pritzel, M.: Mnestic disorders in long-term high-dose diazepam abuse: A pilot study. Eur. J. Psychiatry 9:254–259; 1994.
60. Weinstein, A. M.; Nutt, D. J.: A cognitive dysfunction in anxiety and its amelioration by effective treatment with SSRIs. J. Psychopharmacol. 9:83–89; 1995.
61. Zangrossi, H.; File, S. E.: Behavioral consequences in animal tests of anxiety and exploration of exposure to cat odor. Brain Res. Bull. 29:381–388; 1992.
62. Zangrossi, H.; File, S. E.: Chlordiazepoxide reduces the generalised anxiety, but not the direct responses, of rats exposed to cat odor. Pharmacol. Biochem. Behav. 43:1195–1200; 1992.
63. Zangrossi, H.; File, S. E.: Habituation and generalization of phobic responses to cat odor. Brain Res. Bull. 33:189–194; 1994.
64. Zhu, X.-O.; McNaughton, N.: Effects of long-term administration of anxiolytics on reticular-elicited hippocampal rhythmical slow activity. Neuropharmacology 30:1095–1099; 1991.
65. Zhu, X.-O.; McNaughton, N.: Effects of long-term administration of imipramine on hippocampal rhythmical slow activity. Psychopharmacology 105:433–438; 1991.
66. Zhu, X.-O.; McNaughton, N.: A comparison of the acute effects of a tricyclic and a MAOI antidepressants on septal driving of hippocampal rhythmical slow activity. Psychopharmacology 114: 337–344; 1994.
67. Zhu, X.-O.; McNaughton, N.: Effects of long-term administration of phenelzine on reticular-elicited hippocampal rhythmical slow activity. Neurosci. Res. 21:311–316; 1995.
68. Zhu, X.-O.; McNaughton, N.: Similar effects of buspirone and chlordiazepoxide on a fixed interval schedule with long-term, low-dose administration. J. Psychopharmacol. 9:326–330; 1995.
69. Zhu, X.-O.; McNaughton, N.: Minimal changes with long-term administration of anxiolytics on septal driving of hippocampal rhythmical slow activity. Psychopharmacology 118:93–100; 1995.