Regional dissociations within the hippocampus—memory and anxiety


Abstract

The amnestic effects of hippocampal lesions are well documented, leading to numerous memory-based theories of hippocampal function. It is debatable, however, whether any one of these theories can satisfactorily account for all the consequences of hippocampal damage: Hippocampal lesions also result in behavioural disinhibition and reduced anxiety. A growing number of studies now suggest that these diverse behavioural effects may be associated with different hippocampal subregions. There is evidence for at least two distinct functional domains, although recent neuroanatomical studies suggest this may be an underestimate. Selective lesion studies show that the hippocampus is functionally subdivided along the septotemporal axis into dorsal and ventral regions, each associated with a distinct set of behaviours. Dorsal hippocampus has a preferential role in certain forms of learning and memory, notably spatial learning, but ventral hippocampus may have a preferential role in brain processes associated with anxiety-related behaviours. The latter’s role in emotional processing is also distinct from that of the amygdala, which is associated specifically with fear. Gray and McNaughton’s theory can in principle incorporate these apparently distinct hippocampal functions, and provides a plausible unitary account for the multiple facets of hippocampal function.

Keywords: Hippocampus; Dorsal; Ventral; Amygdala; Spatial; Learning; Memory; Anxiety; Fear; Freezing; Startle

1. Preferentially dorsal hippocampus-dependent functions
2. Preferentially ventral hippocampus-dependent functions
3. Partial hippocampal lesion effects in freezing paradigms and the watermaze
4. Partial hippocampal lesion effects on unconditioned ethologically based tests of anxiety
5. The roles of the ventral hippocampus and amygdala in anxiety-related processes
6. Conclusions
References

The hippocampus has a long-established role in certain forms of memory [117]. However, it has become increasingly apparent that the hippocampus is not just concerned with the formation of memories, but is likely to play a more general role in information processing and the subsequent regulation of behaviour. Recently it has emerged that these various functions may be distributed through the hippocampus. This review outlines what some of these apparently very different functions may be, and how far we can at present localise them to specific hippocampal subregions. We suggest (i) that the dorsal subregion, defined as 50% of hippocampal volume starting at the septal pole [10], and sometimes referred to as posterior hippocampus in primates, has a preferential role in spatial learning and memory, and (ii) that the ventral subregion, defined as 50% of hippocampal volume starting at the temporal pole, and sometimes referred to as anterior hippocampus in primates, may have a preferential role in anxiety-related behaviours. The latter’s role in emotional processing is also distinct from that of the amygdala, which we suggest is associated with fear rather than anxiety. We conclude that Gray and McNaughton’s [56] theory can in principle...
incorporate these apparently distinct hippocampal functions, and provides a plausible unitary account for the multiple facets of hippocampal function [82].

When Scoville and Milner reported that bilateral resection of the medial temporal lobe caused a profound anterograde amnesia in human patients, they initiated a new era of study into the neuropsychology of memory [84]. One focus of that study was the hippocampus, which had been substantially and bilaterally damaged in their most famous patient, H.M. [31,117]. A series of studies in animals sought to determine whether damage restricted to the hippocampus alone could induce a comparable amnesia. Somewhat puzzlingly, the consensus from these studies up until the 1960s was that by and large there was no evidence of a selective amnesia. Animals with large hippocampal lesions apparently learned a variety of new tasks quite normally. Their abnormality lay not in new task acquisition, but in an apparent tendency to persist in these learned responses once they were no longer appropriate. There was evidence of perseverative responding during extinction in a runway [64]; evidence of difficulty in reversal learning [69]; and evidence of excessive responding in operant schedules even when increased lever-pressing led to decreased reinforcement [28]. These kinds of observations led to the formulation of theories of hippocampal function that emphasised its role in behavioural inhibition, an adaptive process whereby organisms suppress responses that are, for some reason, no longer appropriate. On this kind of view, the mechanisms for increasing the probability of positively reinforced responses are segregated from those in the behavioural inhibition system via which the probability of negatively reinforced responses is decreased.

Behavioural inhibition under conditions of conflict had been the focus of a series of studies on the effects of tranquilising drugs, initially investigating the effects of alcohol and barbiturate administration and subsequently including study of the benzodiazepine minor tranquillisers. Moderate doses of these agents appeared to resolve conflict between approach and avoidance tendencies in favour of approach [12]. Thus the effects of minor tranquilliser administration, at least in some respects, paralleled those of hippocampal dysfunction. Gray’s theory of hippocampal function proposed that these parallels arose because the septo-hippocampal system was a core component of the behavioural inhibition system, and went further by identifying the hippocampal theta rhythm (at 7.7 Hz) as the neural substrate of frustrative non-reward [52,55].

The proposal by O’Keefe and Nadel [97] that the hippocampus is the neural substrate of a cognitive map of space, coupled with the development of new spatial memory tasks for rodents—particularly the radial arm and T-maze spatial working memory tasks, and the immensely influential watermaze reference memory task—changed the picture radically [85,86,98,110]. Lesion experiments and single unit recording studies concentrated increasingly on spatial paradigms. The effect sizes [29] of hippocampal lesion-induced changes in performance in these designs can be exceptionally large, as the cognitive map theory would suggest. There seemed to be little room for a hippocampal role in the behavioural inhibition of ongoing behaviour under conditions of fear or anxiety.

1. Preferentially dorsal hippocampus-dependent functions

An opportunity to reconcile these accounts of hippocampal function has arrived with the demonstration that lesions of different hippocampal subregions have distinct and dissociable behavioural effects. A number of early behavioural experiments [60,92,121,119] coupled with anatomical studies demonstrating clear differences in afferent and efferent connectivity along the septotemporal extent of the hippocampus [118,123,133], had hinted at potential differences between dorsal and ventral hippocampus. These suspicions were confirmed with the demonstration by Moser and colleagues [90] that whereas aspiration dorsal hippocampal lesions resembled complete hippocampal lesions in severely disrupting spatial learning in the Morris watermaze, ventral hippocampal lesions of similar size were without effect.

Importantly, in a follow up study, Moser and colleagues replicated these findings but this time using fibre-sparing, ibotenic acid lesions rather than aspiration lesions [91]. Using this approach they made bilateral, symmetrical hippocampal lesions, varying in size from 20 to 100% of the total hippocampal volume, extending from either the septal or temporal pole of the hippocampus. Consistent with their previous findings, they found that although spatial learning was essentially intact with as little as 26% of the dorsal hippocampus still remaining, lesions of the septal pole sparing as much as 60% of the ventral hippocampus, resulted in a robust watermaze impairment. The neurotoxic lesion approach resulted in discrete and specific lesions to the intended area but preserved nerve fibres and cerebrovascularity passing through the lesioned area [63]. Consequently, the resulting behavioural effects could be attributed, with some degree of confidence, to differences in the functions performed by the different hippocampal subregions, and were unlikely to be due to differential effects on fibres of passage coursing through either the septal or temporal pole of the hippocampus.

Since the publication of this finding, a number of studies have now examined the effects of dorsal and ventral hippocampal cytotoxic lesions on spatial learning, in various different learning paradigms, and in general they have revealed similar patterns of results [8–10,70,81]. In addition to impairing spatial reference memory acquisition
in the watermaze, dorsal hippocampal lesions have also been shown to impair spatial learning on appetitive maze tasks such as T-maze rewarded alternation [8,10,59] and performance on a 4/8 radial maze task [106], thus resembling complete hippocampal lesions. In contrast, ventral hippocampal lesions left performance in these tasks unaffected. These appetitive maze studies were important for two reasons. First, they demonstrated that dorsal but not ventral hippocampal lesions still impaired spatial learning under very different experimental conditions from those encountered in the watermaze, with very different sensorimotor and motivational demands (e.g. running vs. swimming; food reward vs. escape from water). Second, they showed that dorsal but not ventral hippocampal lesions impair spatial working as well as spatial reference memory [8,10,59,106].

Several other lines of evidence are also now available to support the conclusion from lesion studies that the dorsal hippocampus has a preferential role in spatial learning and memory. For example, there is now evidence accumulating to suggest that, in spatial memory tasks, acute microinfusions of drugs which temporarily interfere with the normal activity within localised hippocampal subregions yield similar patterns of results to those obtained from lesion studies (e.g. [89,128] McHugh et al., in preparation; Yee et al., in preparation). This is important because microinfusion studies offer fewer opportunities than lesion studies for compensatory changes because the effects of the manipulation are transient and short lasting (see Refs. [13,14], and also permit within subject comparisons. Further evidence from electrophysiological single unit recording studies in both rats [66] and primates [30], from c-fos activation studies [130], and from structural magnetic resonance imaging studies [77], also suggest a functional dissociation between dorsal (posterior in primates) and ventral (anterior in primates, see Refs. [133]) hippocampus, and a preferential role for dorsal hippocampus in spatial learning and memory.

As has been highlighted previously [88], this is entirely consistent with the fact that the major input of visuo-spatial information to the hippocampus from primary sensory cortical areas, via association cortex, and perirhinal and entorhinal areas, is primarily to the dorsal two thirds of the hippocampus [3,24,25,39,40]. In contrast, other types of sensory input (such as olfactory input) are more evenly distributed along the dorsoventral extent of the hippocampus [88]. Thus, in types of hippocampus-dependent memory relying less on spatial, but more on other types of information, such as olfactory cues [22,23], the role of the dorsal hippocampus may be less dominant than in spatial memory. This remains to be examined.

At this point it is important to stress that the distinction between dorsal and ventral hippocampal roles in spatial learning may be preferential rather than absolute in nature. That is to say, the ventral hippocampus may contribute to spatial learning at least under some conditions [38,44,45]. For example, De Hoz and colleagues have recently shown that rats with excitotoxic dorsal hippocampal lesions can eventually acquire a spatial reference memory task in the Morris watermaze if given sufficient training [38]. Because animals with complete hippocampal lesions did not show this improvement in performance, these results suggest that there are conditions under which the ventral hippocampus can contribute effectively to spatial learning. As De Hoz and colleagues point out, this finding is consistent with the fact that ventral as well as dorsal hippocampus exhibits increased c-fos activation after spatial training (albeit proportionately less selectively relative to non-spatial training; [130]), and also with the observation that place cells do exist in the ventral hippocampus (albeit more infrequently and with less well defined place fields; [66,107]). Both of these findings suggest that ventral hippocampus might support spatial learning, albeit generally less effectively than its dorsal counterpart. This functional gradient is consistent with the fact that many anatomical differences in connectivity along the septotemporal axis of the hippocampus are gradual rather than absolute, with a graded pattern of afferent and efferent projections to and from dorsal and ventral hippocampus, rather than marked demarcations [3]. As a consequence, the definitions of dorsal and ventral hippocampus may themselves need further refinement. Moreover, the extensive connectivity between dorsal and ventral hippocampus [2] also predicts some degree of functional interdependence between the two subregions, however defined.

2. Preferentially ventral hippocampus-dependent functions

Identification of clearly dorsal hippocampus-dependent functions (that are largely ventral hippocampus independent) raises the intriguing question as to whether the ventral hippocampus might likewise be preferentially involved in a particular subset of hippocampus-dependent behaviours [59,88]. As was outlined above, the preferential involvement of the dorsal hippocampus in spatial information processing is entirely consistent with its known anatomical connectivity-dorsal hippocampus receives most of the highly pre-processed visuo-spatial information from sensory modalities [88]. The identity of the anatomical connections to and from the ventral hippocampus must surely provide a major clue as to its function. The ventral subregion differs markedly from the dorsal subregion in its anatomical connections. It projects to the prefrontal cortex, whereas the dorsal hippocampus does not [11,49,65,131]. It is closely connected to the bed nucleus of the stria terminalis (BNST) and the amygdala [57,72,102,105,123,129], as well as other subcortical structures which are associated with the hypothalamic-pituitary–adrenal (HPA) axis [3,62,118,123,133]. Most of the amygdalar nuclei have some reciprocal projections with the hippocampal formation, although this is most pronounced for the basal and lateral nuclei [105].
The strong connectivity between ventral hippocampus and both the hypothalamus and the amygdala, makes it tempting to propose a role for the ventral subregion in fear and/or anxiety, and thus potentially account for some of the hippocampal lesion effects on emotionality. One paradigm in which this possibility has been extensively examined is contextually conditioned freezing.

Conditioned freezing in rats is a protective immobility response to conditioned stimuli associated with aversive unconditioned stimuli, such as a foot-shock, and is particularly expressed in a situation where escape is impossible [43]. A number of studies have shown that hippocampal lesions disrupt the acquisition and/or expression of contextually conditioned freezing, although the underlying basis for these effects has been debated at length in recent years [51,83]. There is evidence that ventral hippocampal lesions can be as effective as total hippocampal lesions in reducing the levels of freezing seen after the delivery of a mild foot-shock ([112] but see also Refs. [70]). The reduction in freezing levels was observed both to the tone that had signalled the delivery of the foot-shock and to the experimental context in which the shock had been delivered, and was evident immediately after the delivery of the first foot-shock during the training phase of the experiment. A similar reduction in freezing levels was observed following ventral subiculum lesions [78]. In contrast, Richmond et al. [112] showed that cell loss limited to the dorsal hippocampus had no effect on freezing (see also Refs. [79]). These results led to the suggestion that the ventral, as opposed to the dorsal hippocampus, is preferentially involved in conditioned freezing. The generality of this conclusion is still debated. Possible reasons for discrepancies between different lesion studies, such as distal damage and compensatory processes, have been discussed at length recently [4,5,14,16,70]. Differences in behavioural testing procedures may also be potentially important, and so could themselves merit further attention. Indeed, it may be the case that conditioned freezing is not the optimum paradigm for delineating ventral hippocampal functions in anxiety-related behaviour: other paradigms are considered in a subsequent section.

An alternative approach derives from the use of temporary pharmacological manipulation of dorsal and ventral hippocampus by intracerebral drug microinfusions. These experiments have been taken to indicate that both dorsal and ventral hippocampal subregions can play a role in specific memory processes underlying a normal freezing response in fear conditioning experiments (for review and discussion see Refs. [4,5,14,16,116]). If so, then disruption of these memory processes could account at least for a part of the freezing impairments seen after hippocampal lesions. It is of course important to be able to establish the exact spread of the drug for precise comparison with lesion studies. Moreover, when drugs are administered so as to manipulate acquisition or retrieval only, then the possibility of state-dependent memory impairment must be considered alongside the possibility of specific memory impairment. Given these caveats, it is clearly important to reconcile the results from ablation and temporary activation or inactivation studies.

Finally, it has recently been suggested that the ventral hippocampus may exert control over the expression of conditioned freezing by modulating dopaminergic transmission in the medial prefrontal cortex [99,103]. This proposal extends earlier reports that lesions of discrete prefrontal subfields can interfere with the expression of conditioned fear in rats. The ventral, but not the dorsal, hippocampus enjoys a direct projection to the medial prefrontal cortex and is in a unique position to influence the prefrontal dopamine functions (for review see Ref. [124] and also Ref. [13, p. 334]). This may represent a route whereby the ventral regions of the hippocampus make a distinctive contribution to conditioned freezing.

3. Partial hippocampal lesion effects in freezing paradigms and the watermaze

There is a widely held notion that spatial learning, as exemplified by tasks such as the Morris watermaze, and contextual fear conditioning are essentially different manifestations of the same basic underlying process [80,93,97,115,122]. Such a line of thought is tempting because there is an intuitive similarity between these spatial and contextual forms of learning in that both are likely to involve processing, perhaps integrating, complex stimuli which are often large [27], diffuse, multicue, polymodal, and relational [16]. However, there are differences in their sensitivities to partial hippocampal lesions, and certain pharmacological manipulations, consistent with differences in their underlying neural substrates within the hippocampal system [10,14,112].

When lesions are made before training, cytotoxic dorsal lesions appear to disrupt spatial learning more consistently and effectively than ventral ones. Conversely, cytotoxic dorsal lesions appear to disrupt contextually conditioned freezing less reliably than ventral ones. When lesions made after training are considered, there is an intriguing analogy between the differences in antero- and retrograde effects of partial hippocampal lesions on contextual fear-conditioning and in watermaze experiments. Contextual fear conditioning seems to be more susceptible to selective dorsal hippocampal lesions if they are made between training and testing, than if they are made before training [4,79]. An analogous result has been obtained for ventral hippocampal lesions and spatial learning in the watermaze [89]. As with contextual fear conditioning, memories acquired prior to the lesion were affected by a degree of hippocampal damage that was without effect on the acquisition of new memories. Partial hippocampal lesions restricted to the ventral 40% of the hippocampus disrupted the retrieval of a previously acquired spatial reference memory task in the watermaze,
but then had no effect on the acquisition of a second spatial task in a novel environment. The retrograde effects both of ventral hippocampal lesions on spatial learning in the watermaze and of dorsal hippocampal lesions on contextual freezing, coupled with the absence of equivalent anterograde effects, suggest that under normal circumstances these memories may be encoded and subsequently retrieved by widely distributed networks extending beyond a more crucial—or even obligate—zone into a substantial portion of the remainder of the hippocampus. However, acquisition of new memories and their subsequent retrieval can be achieved with more limited neuronal networks when partial lesions are made before learning. Under these circumstances different hippocampal subregions preferentially support the acquisition of spatial learning and of contextual freezing.

4. Partial hippocampal lesion effects on unconditioned ethologically based tests of anxiety

The possibility that the ventral hippocampus may have a specialised role in fear or anxiety related behaviours has also recently been examined using a series of unconditioned anxiety tests [81]. This study had two goals. First, it extended the comparison of the effect of dorsal and ventral hippocampal lesions to examine the generality of the inferences derived from freezing studies. Second, a group of animals with cytotoxic lesions of the amygdalar complex (intended to include all the major amygdala nuclei) was included for direct comparison with the effects of hippocampal lesions to determine whether these two brain areas contribute differentially to fear and anxiety.

Ventral hippocampal lesions had behavioural effects resembling those induced by benzodiazepines on these tasks, consistent with a reduction of anxiety (see Ref. [56], Appendix 1). In agreement with previous studies, rats with selective ventral hippocampal lesions (i) showed reduced hyponephagia, i.e. they were quicker to eat in potentially anxiogenic, unfamiliar environments (see also Refs. [8,9]; (ii) displayed increased social interaction (see also Ref. [8]); (iii) were quicker to cross from the black to the white compartment during a two compartment box test, and (iv) spent an increased proportion of time in a more anxiogenic section of the successive alleys apparatus, a modified version of the elevated plus maze (see also Refs. [8,70]). On each of these four very different behavioural tests, the ventral hippocampal lesions had effects that are consistent with an anxiolytic effect.

Animals with ventral hippocampal damage differed from those with dorsal hippocampal lesions on these tests. The latter generally displayed little, if any, effect on tests of anxiety, relative to the sham operated controls [8,70,81]. Rats with dorsal hippocampal lesions did, however, display a marked spatial learning impairment in the Morris water-maze, unlike the ventral lesioned rats whose spatial learning performance was indistinguishable from the controls. This therefore provides a clear double dissociation of the effects of dorsal and ventral hippocampal lesions on spatial learning and a range of ethologically based tests of anxiety. A double dissociation was also observed for the dorsal and ventral lesion groups between the anxiety tests and spontaneous locomotor activity as measured in photocell activity cages [8,81]. This is important because lesion-induced hyperactivity is a potential confound of all of these anxiety tests, as well as of conditioned freezing tests [51]. This double dissociation suggests that a simple account based on a general hyperactivity in lesioned animals cannot adequately explain the pattern of results obtained here. Note that we and others have also observed other effects of ventral hippocampal lesions which are consistent with reduced anxiety and which do not rely on measures of activity. For example, there is good evidence that high levels of anxiety are associated with increased defaecation [20,21,53,54]. We have observed reduced levels of defaecation in ventral hippocampal lesioned rats, both in a brightly illuminated open field test and at certain stages of contextual fear conditioning and its subsequent extinction, although importantly there were no differences between sham and lesioned animals in defaecation levels in the home cage [9]. A similar observation was made by Kjelstrup and colleagues who reported that both complete and ventral hippocampal lesions reduced defaecation scores relative to sham and dorsal hippocampal lesioned animals following confinement in a brightly lit white chamber [70]. In addition, they also found that ventral lesioned animals showed a reduced increase in plasma corticosterone concentrations 20 min after the confinement, as compared to controls (see also Ref. [128]; but note also Ref. [58]). Both of these results suggest that the effects of ventral hippocampal lesions extend beyond a mere disinhibition of motor activity under anxiogenic conditions, indicating a more central role for this brain area in anxiety.

5. The roles of the ventral hippocampus and amygdala in anxiety-related processes

Direct comparison between the effects of amygdala lesions and ventral hippocampal lesions revealed a number of important and notable distinctions. Amygdala lesions had no effect on the successive alleys test, a result which is consistent with several previous demonstrations that these lesions, in contrast to hippocampal damage, have no effect on performance on the elevated plus maze [37,70,120, 125–127]. Amygdala lesions also had no significant effect on social interaction (to the extent that there was any change it was in the opposite direction to rats with ventral hippocampal lesions: their levels of social interaction were slightly lower than those observed in sham operated animals). On the hyponephagia tests, the amygdala lesioned animals took significantly longer to begin eating, an effect which was once again
in the opposite direction to that seen with ventral hippocampal lesions. Indeed the only test on which the amygdala and ventral hippocampal lesions resulted in comparable effects was the black/white two-compartment box test.

These results clearly demonstrate that the effects of ventral hippocampal lesions are, at least in some respects, distinct from those of amygdala lesions. These observations are important, firstly because they demonstrate that the behavioural effects of ventral hippocampal lesions are not simply a consequence of either direct or indirect effects on the amygdala (e.g. unintended incidental damage or de-afferentation), and secondly because they clearly indicate that the ventral hippocampus and the amygdala contribute differentially to the processing of fearful or anxiogenic stimuli, despite having similar effects on some measures of conditioned freezing [61,104,112].

Several additional lines of evidence support the idea that the amygdala, unlike the hippocampus, is not crucial for normal performance during anxiety tests such as the elevated plus maze. In addition to the clear absence of amygdalar lesion effects on this test under normal conditions, they also fail to block the anxiolytic effects of systemic benzodiazepine treatment on this apparatus if a single test is conducted ([127]; see also Ref. [47]). It is also worth noting that, in general, infusion of benzodiazepines directly into the amygdala has no effect on plus maze performance ([50,100]; but see also Refs. [101]), although it does produce apparently anxiolytic effects in at least some test paradigms [94], and there is a high density of benzodiazepine binding sites in the amygdala [95,96]. There is, however, a clear role for the hippocampal formation during elevated plus maze testing. In addition to the recent demonstrations of ventral hippocampal lesion effects on plus maze performance [8,70,81], there are several reports of anxiolytic effects of both complete hippocampal and septal lesions on this task [36,37,125,126].

The idea that the hippocampus and amygdala contribute differentially to mechanisms underlying fear and anxiety is not novel [56]. While it is apparent that anxiety and fear are intimately related and overlapping, it is now widely accepted that they should not be considered as a unitary construct [35,46,56,109]. According to Davis and colleagues, fear is a phasic response to explicit, often conditioned, aversive cues, while anxiety is a more tonic response to rather diffuse, often unconditioned, aversive cues or situations [35]. Gray and McNaughton [56] similarly propose that fear is associated with (more phasic) active avoidance or escape responses and removal from a dangerous situation. Anxiety, on the other hand, may result from diffuse aversive stimuli; is associated with conflict and uncertainty (e.g. whether or not an animal should enter/ approach a potentially dangerous situation); and results when there is competition between concurrently available goals. They further propose that fear may often be viewed as a logical precursor of anxiety, and that there is a hierarchical organization with anxiety systems providing an inhibitory control over fear systems.

A further line of evidence that also indicates separate roles for the hippocampus and amygdala in fear or anxiety-related behaviours derives from studies of potentiated startle. The acoustic startle reflex is a rapid contraction of the skeletal muscles elicited by a sudden auditory stimulus and is assumed to be an unconditioned protective reaction. The startle reflex is mediated by a brain-stem circuit [34,134], but modulated by forebrain sites [71]. For example, the BNST and the amygdala, which are both closely linked to the ventral hippocampus [105,123], have access to the startle circuit and exert control over it [35,71]. Importantly, emotional states exert a strong influence on startle reactivity [71,73]: enhanced startle reactivity is a diagnostic criterion for anxiety disorders in humans and is used as an animal model of anxiety [35,114]. According to the concept of emotional priming, the startle response as a protective reaction to an aversive and threatening stimulus may be enhanced by negative and attenuated by positive emotional states [73]. For example, in the conditioned fear-potentiated startle paradigm rats are first trained to be fearful of a light CS predicting footshock. Conditioned fear to the light is then indexed by the elevation of startle response in the presence of the light relative to that in its absence. The fear-potentiated startle effect is blocked by amygdala lesions [33,34,35].

Hippocampal lesions do not reliably affect basal startle magnitude (e.g. [67,74–76,108, for review, see Ref. [13]). Localized microinfusions of a wide range of drugs (e.g. NMDA, tetrodotoxin, muscimol, picrotoxin) into either the dorsal or ventral subregions all tended to attenuate the startle response [15,17,132,136,137], with the exception of dorsal hippocampal infusion of the non-competitive NMDA receptor antagonist, MK-801, which potentiated basal startle reactivity [6,7,135]. Thus no regionally or neuropharmacologically specific hippocampal role has been identified in basal startle responding, at least when startle reactivity is evaluated in an emotionally relatively neutral situation.

A rather different picture emerges when startle is elicited in an anxious state, induced using a pharmacological manipulation in the form of intracerebroventricular (i.c.v.) microinfusion of corticotropin-releasing hormone (CRH). Intraventricular CRH infusion elicits a syndrome that resembles the effects of stress or anxiety [41]. This encompasses physiological, endocrinological and behavioural changes, including an increase in startle amplitude. There is now increasing evidence that the hippocampal formation in combination with the BNST represents the neural system that underlies CRH-enhanced startle [75,76]. For example, transection of the fimbria with a knife cut resulted in an almost complete blockade of CRH-enhanced startle [75]. The same study showed that electrolytic dorsal hippocampal lesions did not affect CRH-enhanced startle, suggesting that if the hippocampus is involved then it is
likely to be the ventral and not the dorsal hippocampus that is important (so long as the fimbria itself was left unaffected by the dorsal lesions). Indeed, Lee and Davis concluded from this study that the effects of fimbria-fornical transection on CRH-enhanced startle were likely to be due to the disruption of a well documented fibre pathway from the ventral hippocampus to the BNST [3, 26, 32, 123], which in turn then projects to the neural circuitry underlying the startle reflex.

In a subsequent study they demonstrated that the primary site of action of CRH is likely to be the BNST. Interestingly, although cytotoxic lesions of the BNST completely blocked CRH-enhanced startle, they had no effect on the acquisition of the classical fear-potentiated startle response to an explicit visual CS. In contrast, cytotoxic lesions of either the central or basolateral nuclei of the amygdala, which did block fear potentiated startle, had no effect on CRH-enhanced startle. This double dissociation between the effects of BNST and amygdala lesions on the two variants of enhanced startle provides a plausible unitary account of hippocampal involvement in anxiety as distinct from fear, which more plausibly depends on amygdalar function. Such a view could coexist with views that allocate a specialised role to the dorsal region of the hippocampus in spatial learning, while at the same time specifying at least one way in which the role of the hippocampus extends beyond the purely spatial domain and into the anxiety related behaviours that were at the core of Gray’s behavioural inhibition theory [55, 56].

Furthermore, it seems increasingly likely that even the mnemonic functions of the hippocampus are not restricted to the spatial domain. The hippocampal memory system may provide the means for encoding both the spatial and temporal contexts (the ‘where’ and the ‘when’) associated with a particular event, thus capturing the key properties associated with episodic memory in humans [42, 87]. There are several recent demonstrations of hippocampal involvement in the temporal sequencing of events [1, 48, 68]. A major challenge that now remains is to identify a common psychological operation that might underlie both an episodic-like memory function and a role in anxiety. Gray and McNaughton’s theory can in principle incorporate these apparently very different hippocampal roles, thus providing a plausible unitary account of hippocampal function [56]; see also Ref. [82], this issue). They suggest that the algorithm performed by the hippocampus is to compare different potential response alternatives and then to select the optimal response. In the case of episodic-like memory tasks, this will involve using conditional information provided by either spatial or temporal cues, or both, to select the appropriate learned response. In the case of unconditioned tests of anxiety, this may involve selecting between conflicting approach and avoid responses, whether it be a novel foodstuff in a novel environment, or the open arms of an elevated plus maze.

Theories of hippocampal function need to identify the different domains within which the hippocampus plays a key role. We believe at least two such domains have already been identified, and further analysis may well identify more, as suggested elsewhere [102, 113]. Although these domains apparently depend preferentially on different hippocampal subregions, we would surely want a truly unifying theory of hippocampal function to explain its role within these domains by reference to a consistent physiological algorithm performed by the intra-hippocampal circuitry.
This would enable the consequences of subfield-specific interventions to be predicted for each domain. Gene-targeted manipulations that modify specific forms of synaptic plasticity have already been shown to result in striking dissociations within the domain of spatial learning and memory [111]. A unifying theory should also allow us to define the kinds of dissociations that these manipulations will bring about in other aspects of hippocampus-dependent information processing.

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