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NEWS & VIEWS

Functional segregation within the human hippocampus

Recent evidence suggests that the functions of the brain region critical for long-term memory, the hippocampus, may be segregated along its anterior-posterior axis.

Since the 1950s, it has been known that hippocampal lesions impair conscious, long-term memory function.[1] Hippocampal damage leads to an amnesic syndrome, characterised by an inability to form any new episodic memories (a dense anterograde amnesia) plus retrograde amnesia for memories acquired premordibly. The extent of the retrograde amnesia is variable and can last up to 20 years, with the general pattern that more recent events are most severely affected, whereas older, well-rehearsed memories remain intact. The development of animal models to mimic hippocampal lesions, as well as animal *in vivo* neuronal recordings, provide evidence that discrete components of hippocampus and medial temporal cortices serve specific functions in forming long-lasting traces of events.[2,3] In humans, the left medial temporal lobe has been shown to be critical for verbal memory and the right for spatial memory.[4,5] Nevertheless, dissociating whether medial temporal function encompasses initial encoding of information, its consolidation or subsequent retrieval still eludes neuroscience, despite a number of proposed theories.

An efficient memory system is one which is able to detect and process novel stimuli.[6] The role of the human hippocampus in novelty detection has been demonstrated by human *in vivo* recordings,[7] event-related potential studies[8,9] and functional imaging studies. Dolan and Fletcher[10] found left anterior hippocampal activation to be maximal during the encoding of novel category-exemplar word pairings, and a later positron emission tomography (PET) study also found left hippocampal activation during encoding of words that were novel in the experimental context.[11] The presentation of novel pictures has also been shown to evoke hippocampal/parahippocampal activation either bilaterally[12,13] or limited to the right.[14]

Attention has now focused on segregating hippocampal function on the basis of anatomy,[15,16] given recent evidence that distinct regions of the hippocampus in rats[17] and humans are functionally specialised. A recent meta-analysis[15] of PET studies of episodic memory found that anterior regions of the hippocampus are preferentially engaged during encoding whereas posterior hippocampal regions are more activated during retrieval, summarised as the HIPER (hippocampal encoding and retrieval) model. Using functional magnetic resonance imaging (fMRI), we have recently demonstrated anterior-posterior functional segregation within the human hippocampus in the processing of relative familiarity.[18] Within the context of an item-learning paradigm, two types of novelty were periodically introduced: perceptual novelty, pertaining to the physical characteristics of stimuli and not behaviourly relevant; and exemplar novelty, reflecting the status of stimuli within a rule system which was behaviourally relevant. The stimuli were four consonant letter strings generated using an artificial grammar system, a set of arbitrary rules governing the concatenation of symbols.[19] Traditionally, artificial grammar systems have been used to assess implicit learning. However, we used a modified approach with an emphasis on explicit learning.

Upon presentation of exemplars of the grammar system, subjects were required to make a push-button response to indicate whether they thought the exemplar was grammatical or ungrammatical and were provided with immediate visual feedback on their judgement. Exemplars were presented repeatedly hence, as exemplars became familiar, subjects could use previous feedback to enhance subsequent performance. In the initial stages of the experiment subjects had no knowledge of the underlying rules of the grammar and responded by guessing. Each set of 10 exemplars was presented eight times and grammaticality judgements improved as subjects became increasingly familiar with each set of exemplars. After the eight presentations a completely new set of

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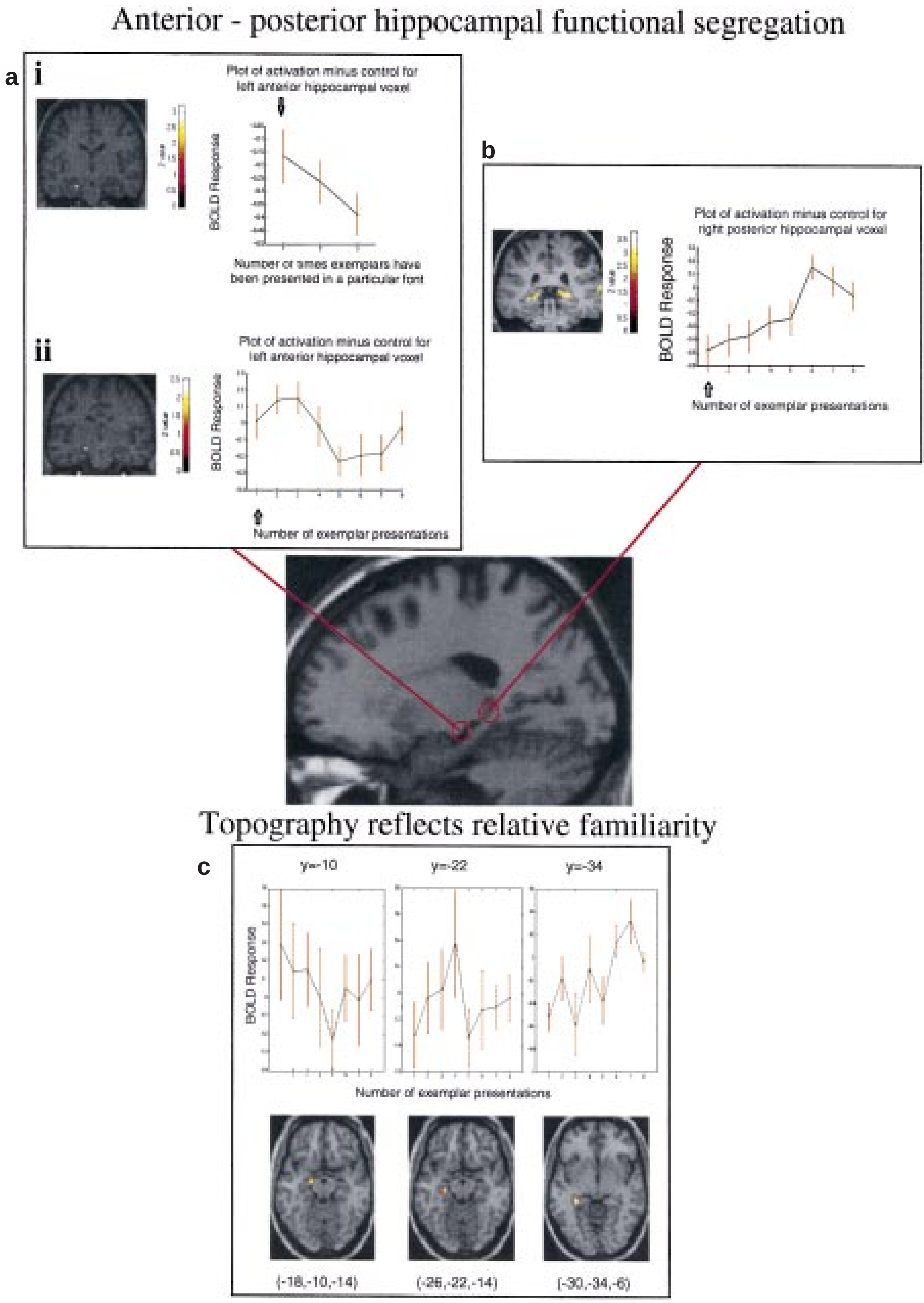
Figure 1 Functional segregation within the human hippocampus for relative familiarity. (a) Left anterior hippocampal activation for: (i) perceptual; and (ii) exemplar novelty showing adaptation with familiarity. (b) Bilateral posterior hippocampal activation with exemplar familiarity. (c) Topography in the anterior-posterior hippocampal axis reflects relative familarity. Note that the term hippocampus is used to refer to the dentate gyrus, CA subfields and subiculum (adapted from Strange *et al*[18]).


Anterior - posterior hippocampal functional segregation
a i
Plot of activation minus control for left anterior hippocampal voxel
BOLD Response
Number of times exemplars have been presented in a particular font
ii
Plot of activation minus control for left anterior hippocampal voxel
BOLD Response
Number of exemplar presentations
b
Plot of activation minus control for right posterior hippocampal voxel
BOLD Response
Number of exemplar presentations
Topography reflects relative familiarity
c
y=-10
y=-22
y=-34
BOLD Response
Number of exemplar presentations
(-18,-10,-14)
(-26,-22,-14)
(-30,-34,-6)

exemplars was presented, allowing the introduction of exemplar novelty. In addition, after every three presentations of an exemplar set, the font in which exemplars were presented was changed, hence introducing perceptual novelty. Critically, the manipulations of exemplar and perceptual novelty were orthogonal (ie uncorrelated), thus enabling separable characterisation of hippocampal responses associated with each type of novelty.

Perceptual novelty enhanced activation in the left anterior hippocampus. A greater left anterior hippocampal response was seen for initial, relative to repeated, presentations of perceptually novel items, reflected in a significant linear time by condition interaction (Figure 1a(i)). Exemplar novelty also produced enhanced activation in the left anterior hippocampus which showed exponential adaptation with exemplar familiarity (Figure 1a(ii)). By contrast, increasing familiarity for exemplars enhanced activation in posterior hippocampus bilaterally (Figure 1b). Increasing font familiarity, which had no behavioural relevance, did not engage the posterior hippocampus. As both perceptual and exemplar novelty were found to engage the left anterior hippocampus, these data suggest that the left anterior hippocampus indexes generic novelty. The posterior hippocampus was only engaged by familiarity with exemplars, hence posterior hippocampal responses index familiarity with items that require processing on the basis of meaning.

In support of our finding of functional segregation within the hippocampus for novel and familiar arrangements of letter strings, Wan *et al*[20] demonstrate that neurones in area CA1 of the rat hippocampus are sensitive to novel arrangements of stimuli, whereas neurones in the dentate gyrus and subiculum are sensitive to familiar arrangements. Functional imaging is not yet capable of reliably discriminating hippocampal subfields but it will be interesting to determine whether cellular recordings in primates reveal similar dissociations along the hippocampal anterior-posterior axis.

Although our study addressed novelty, if novelty and familiarity in our item learning paradigm are considered to involve an emphasis on encoding and retrieval, respectively, our data provide support for the HIPER model[15] described earlier. A recent review of data from fMRI studies[16] concluded, however, that the posterior medial temporal lobe is associated with episodic encoding. However, the majority of encoding-related posterior medial temporal lobe (MTL) activations were located in the parahippocampal gyrus[12,13,21–26] whereas fewer encoding-related fMRI activations have been found in the posterior hippocampus.[12,23,24,27] In contrast, the majority of anterior MTL encoding-related activations included in the Lepage *et al*[15] PET meta-analysis are focused within the hippocampus. It may, therefore, be the case that encoding engages both the anterior hippocampus and the parahippocampal cortex.

The sparing of remote memories in amnesia led to the conclusion that the hippocampus plays only a temporary role in episodic memory, after which information is gradually transferred to the neocortex.[28] A recent theory of hippocampal function[29] has challenged this view proposing, instead, that the hippocampus is always necessary for retrieval of episodes and the context in which they occurred. The 'multiple-trace theory'[29] states that the reactivation and rehearsal of memories causes the formation of multiple memory 'traces' within the hippocampus. A 'trace' could be described as a hippocampal neuronal assembly constituting a junction that binds together information processed in dispersed neocortical areas. The greater the hippocampal damage, the more 'traces' of a particular memory will be lost, which could explain the observed correlation of severity of retrograde amnesia with extent of hippocampal lesion.[30,31]

Our data[18] provide evidence that with increasing familiarity for exemplars, there is a topographical spread of activation posteriorly along the anterior-posterior axis of the hippocampus (Figure 1c). This finding, if confirmed, provides support for the 'multiple-trace theory' and suggests that these 'traces' are organised in a topographical manner. Given the anterior-posterior familiarity gradient, the temporal extent of retrograde amnesia may reflect the posterior extent of hippocampal damage. The left anterior hippocampal role in processing new items could suggest that anterior lesions give rise to the anterograde component of the amnesic syndrome. Interestingly, the famous amnesic patient HM,[1] who had bilateral resection of anterior hippocampus but sparing of posterior hippocampus,[32] had dense anterograde amnesia but was able to recall memories acquired before surgery. Furthermore, the patient NT[33] who had a bilateral lesion along the entire anterior-posterior axis of the hippocampus, did not exhibit characteristic sparing of remote memories and showed retrograde amnesia for all time periods tested.

In conclusion, the finding of functional segregation within the hippocampus for relative familiarity, together with results from meta-analyses of functional imaging studies of memory, will aid understanding of the nature of memory deficits following hippocampal damage. It will be interesting to determine how specific neurotransmitter inputs map to the observed functional segregation. Levels of anterogradely-labelled acetylcholinesterase are greatest in anterior hippocampus, decreasing at more posterior levels.[34] It has been observed that novelty raises hippocampal acetylcholine levels in rats.[35] Furthermore, it has been demonstrated that dopamine D2 receptors are expressed as a double gradient in the human hippocampus, with the dentate gyrus and CA3/4 expressing a greater number of D2 receptors in anterior hippocampus relative to posterior, but the subiculum showing the reverse gradient.[36] Pharmacological manipulations during functional imaging studies of the hippocampus may provide valuable insight into the mechanisms underlying how functional segregation within the human hippocampus is realised.

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