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# Plasticity of hippocampal memories in humans

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The human hippocampus is a brain region that supports episodic and spatial memory. Recent experiments have drawn on animal research and computational modelling to reveal how the unique computations and representations of the hippocampus support episodic and spatial memory. Invasive electrophysiological recordings and non-invasive functional brain imaging have provided evidence for the rapid formation of hippocampal representations, as well as the ability of the hippocampus to both pattern-separate and pattern-complete input from the neocortex. Further, recent evidence has shown that hippocampal representations are in constant flux, undergoing a continual process of strengthening, weakening and altering. This research offers a glimpse into the highly plastic and flexible nature of the human hippocampal system in relation to episodic memory.

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## Introduction

Patients with lesions to the hippocampus have marked deficits in episodic [1] and spatial [2] memory. In particular, selective hippocampal damage, without damage to the surrounding medial temporal lobes (MTL), disrupts performance in tasks that test memory for multimodal associations [3,4] and relational representations [5,6]. Thus, the hippocampus is thought to support the *recollection* [7] of episodic events by representing the complex spatiotemporal patterns that uniquely define typical real-world events.

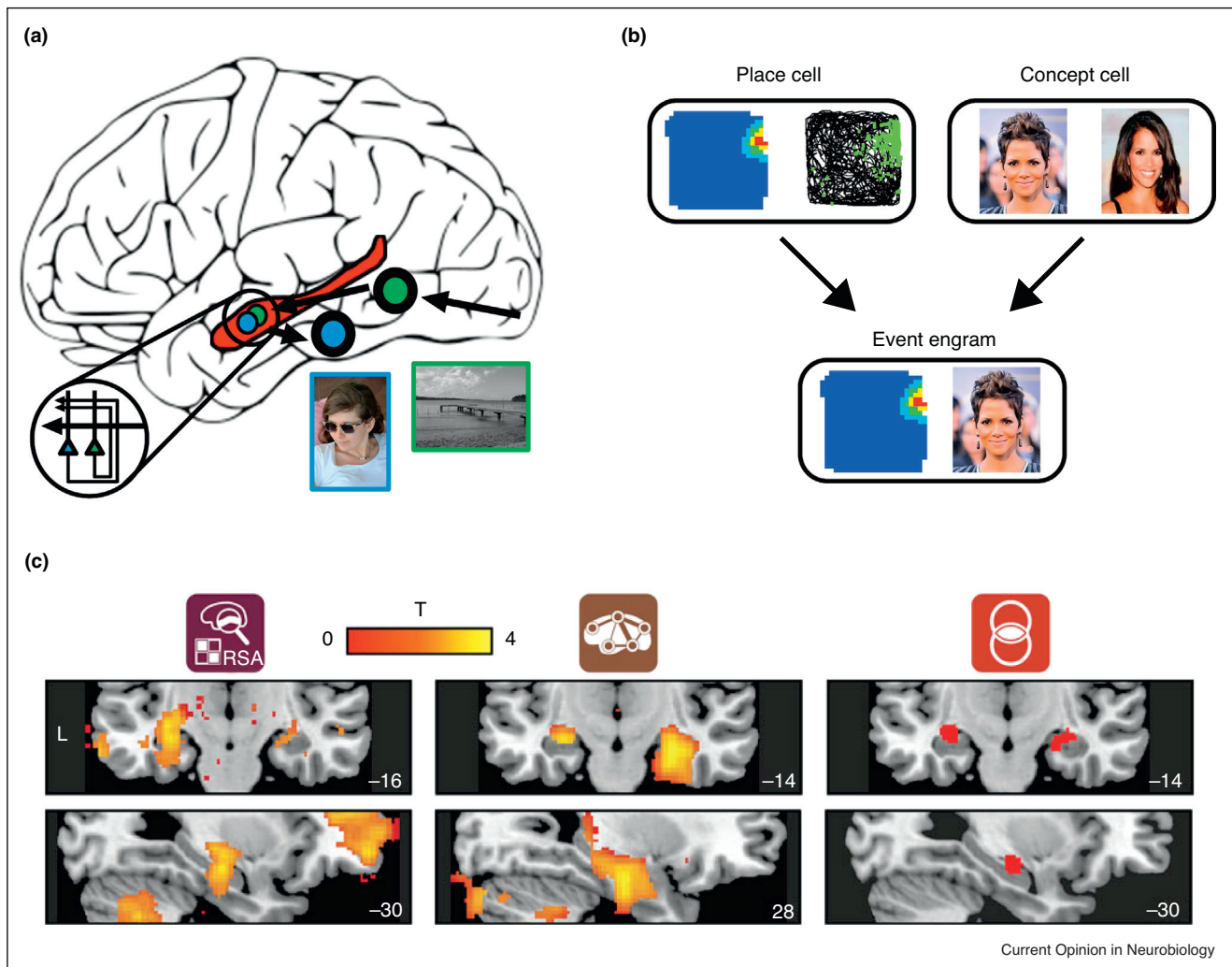
More recently, focus has shifted from the representations supported by the human hippocampus to the computations it performs. These were first postulated in the seminal work of Marr [8], and have been further developed in recent decades [9–11]. This computational approach has been highly influential in the study of the rodent hippocampus [12–14], however it is only recently that it has informed research into the human hippocampus. The principle tenets of this approach are that the hippocampus is able to: (1) rapidly form associations between arbitrary stimuli—*one-shot learning*, (2) form distinct representations despite similar input from the neocortex—*pattern separation*, and (3) retrieve a complete representation in the presence of an ambiguous or partial input—*pattern completion*.

Despite the difficulties associated with studying learning-related plasticity in the human hippocampus, direct, invasive, electrophysiology as well as indirect, non-invasive, functional brain imaging allows us to infer the presence of these processes. Here we review recent electrophysiology and brain imaging studies in humans that reveal both the representational content and computations performed by the hippocampus. We focus on the three tenets of the computational model outlined above. Further, we discuss recent research that extends the role of the hippocampus, from encoding and retrieving distinct episodic memories, to modifying and integrating pre-existing memories into network-like mnemonic structures. This new avenue of research has highlighted the highly plastic and dynamic nature of the hippocampus. Ultimately, it is this flexibility that ensures our memories of the past are continually relevant to decision-making processes in the present.

## Rapid learning in the human hippocampus

No two real-world events are identical; each one is uniquely defined by its complex spatiotemporal characteristics. The individual elements of an event, such as the location you are in or the person you are talking to, are thought to be represented in distinct neocortical regions. The hippocampus is thought to receive input from these neocortical regions, acting as a *convergence zone* [15], rapidly binding together this multimodal information into a coherent *event engram* (Figure 1a,b) [8]—a population of interconnected hippocampal neurons that represent the constituent elements of a specific event. Combining connectivity and pattern similarity measures of fMRI, recent research suggests that the human hippocampus represents associations between multimodal stimuli, whilst simultaneously acting as a ‘hub’ within an extended cortical network, during memory retrieval (Figure 1c)

Figure 1



Event engrams in the human hippocampus. **(a)** Schematic of computational model of episodic memory. Distinct neocortical representations for event elements (e.g. locations and people) form links with individual neurons in the hippocampus (e.g. place and 'concept' cells). When experienced together, hippocampal place cells (green) and concept cells (blue) can rapidly form direct associations, forming 'event engrams'. At retrieval, when the location is cued, the hippocampus receives a partial input. All associated elements are retrieved via the process of pattern completion, supported by the recurrent connections of subfield CA3 (simplified wiring diagram of CA3 in zoomed in panel in bottom left) and subsequently the retrieved elements are reinstated in the neocortex, allowing for the experience of 'recollection'. **(b)** Simplified example of an 'event engram'. Place cells (example shown from a rodent, showing firing in the top right corner of the environment, with permission from Ref. [66]) and concept cells (e.g. a neuron that fires when presented with any image of Halle Berry) may act as the 'building blocks' of episodic memory, the formation of an 'event engram' results from these cells forming direct associations when experienced together, such that the associated concept cell will fire when the place cell fires (and vice versa). Note, event engrams are likely to be much more complex in nature than simple pairwise associations, and may include multiple (*i.e.* >2) elements, with direct connections between the neurons coding for each constituent element. **(c)** Evidence for the 'convergence zone' hypothesis—multivariate and graph-theoretic network analyses suggest the hippocampus represents multimodal pairwise associations (left) and demonstrates 'hub-like' properties (middle) during episodic retrieval (conjunction shown on right; with permission from Ref. [16\*\*]).

[16\*\*], providing experimental evidence for Marr's proposal [8\*].

What form do these hippocampal event engrams take and how rapidly are they established? Invasive electrophysiological recordings of single neurons in the human hippocampus of patients with epilepsy have demonstrated the

presence of cells that fire in response to unique environmental features. In line with rodent research [17], single neurons fire in relation to specific locations in virtual reality (VR) environments [18]. The existence of *place cells* and other spatially modulated neurons in the human hippocampus [19,20], alongside fMRI studies of spatial/scene processing [21,22\*,23,24\*,25], confirm the spatial

nature of representations in the hippocampus and surrounding MTL.

Neurons with non-spatial firing patterns have also been shown, specifically in relation to well-known celebrities, famous buildings, and animals [26<sup>•</sup>,27]. These so-called *concept cells* can respond to the identity of a person in a stimulus-invariant manner. For example, one neuron was shown to respond to both the written name, and a photo of, Halle Berry [26<sup>•</sup>]. Despite ongoing debate concerning how such neurons are best conceptualised [28–30], recent evidence suggests they could potentially represent long-term real world (perhaps not task-specific) associations [31]. As such, they may represent non-spatial environmental features in an analogous manner to spatially modulated place cells—that is, in a stimulus-invariant manner over relatively long times-scales. The presence of both spatial and non-spatial cells that code for specific elements (*e.g.* locations and people) in the real world appears to provide the ideal ‘building blocks’ [32] for event engrams (Figure 1b). In short, event engrams can be rapidly formed via direct associations between hippocampal neurons coding for the individual elements of any specific event.

Importantly, these neurons appear to tune their respective firing fields relatively quickly. Concept cells can respond to individual researchers that the patient only met on the day of testing [33], and recent rodent research has shown that place cell firing fields become tuned after only a single visit to that specific location [34<sup>••</sup>]. Thus, at the level of individual neurons, the hippocampus represents any possibly behaviourally relevant element in the environment, and these representations can be formed rapidly.

Events are more complex than single locations or individuals though. The hippocampus therefore needs to rapidly form direct associations between these neurons. For example, if you met Halle Berry at the Eiffel Tower, the hippocampus needs to form an association between the neurons coding for both of these elements from that single encounter. Recent electrophysiology has shown that individual neurons, which initially fire selectively to a famous person and landmark, change their firing properties after exposure to a composite image (*i.e.* an image of both the person and landmark) such that they subsequently fire to either image in isolation [35<sup>••</sup>]. Further, following an object-location encoding task in a VR environment, place cells associated with the location of a specific object were shown to fire during a free recall task when participants recalled that specific object [36]. These studies suggest the rapid formation of direct associations between neurons in the hippocampus, supporting the subsequent retrieval of an episodic-like memory.

Real word events are more complex in nature than the simple pairwise associations tested in the studies

presented above, involving multiple elements that form complex configural representations. Nonetheless, the studies support the concept that the hippocampus acts as a convergence zone, rapidly forming associations between stimuli represented in distinct neocortical regions. However, one critical outstanding question is how such hippocampal neurons continue to differentiate between specific elements in the environment—once Halle Berry has been seen at the Eiffel Tower, how is the hippocampus able to independently represent Halle Berry and the Eiffel Tower (allowing them to be separately incorporated into future events), whilst simultaneously maintaining a configural representation of the two elements?

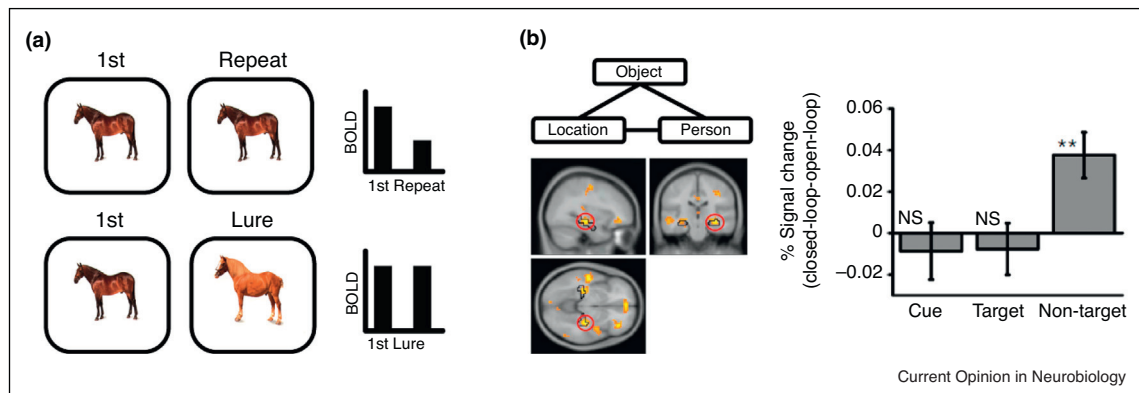
### Pattern separation and pattern completion in the human hippocampus

Pattern separation refers to the production of distinct (orthogonal) non-overlapping representations from similar overlapping input. It decreases interference at retrieval by minimising the representational overlap between two similar events at encoding. The dentate gyrus (DG), with its large number of neurons (relative to its principal input, the entorhinal cortex) and sparse coding, is thought to primarily support pattern separation in the hippocampus.

fMRI has been used to provide evidence for pattern separation in the human hippocampus [37<sup>•</sup>]. The presence of pattern separation should mean that similar stimuli, for example two different images of an apple, are encoded as distinct representations. The authors used the well-known effect of adaptation, where repetition of the same stimulus results in reduced BOLD responses, to infer the presence of pattern separation. They took a release from adaptation when presented with a similar, but not identical, stimulus as a marker for pattern separation (Figure 2a). They saw this effect in a combined DG/CA3 region, but not in CA1 or surrounding MTL regions. Further studies have parametrically manipulated the similarity of repeated stimuli to show a non-linear mapping between the input and output of the hippocampus [38,39], consistent with a pattern separation process. However, the studies presented pictures of objects rather than more complex events known to be supported by the hippocampus. Further, the results may be explicable in terms of a ‘match-mismatch’ signal unrelated to pattern separation [40].

More recently, videos of events with overlapping content have been combined with multivariate analyses of fMRI to provide further evidence of pattern separation [41]. By orthogonally combining two background contexts (scenes) with two foreground ‘events’ (people with objects), creating four related videos, the authors showed that representations in the hippocampus successfully distinguished each individual video. Further, multivariate

Figure 2



Pattern separation and pattern completion. **(a)** Evidence for pattern separation in the human hippocampus was first shown by Bakker *et al.* The repetition of a stimulus leads to the well-known phenomenon of adaptation, or repetition suppression. However, when a similar looking 'lure' image is shown, DG showed a BOLD response similar to the first presentation of the image (see Ref. [37] for details). This suggests that DG is pattern separating the 'lure' image—encoding it as a separate representation despite the similar perceptual input. Example shown is illustrative, and does not present actual stimuli used or data presented. **(b)** Evidence for pattern completion in the human hippocampus has recently been shown by Horner *et al.* After learning location-object-person events (across three separate encoding trials, see Ref. [50\*\*] for details), participants were tested on specific pairwise associations (e.g. cue location, retrieve object). Neocortical reinstatement was critically shown for the 'non-target' elements (e.g. person), suggesting all elements were retrieved and reinstated in the neocortex. Critically, the amount of reinstatement for 'non-target' event elements correlated with hippocampal BOLD response at retrieval, consistent with the proposal that the hippocampus retrieves all event elements via pattern completion, leading to their reinstatement in the neocortex (hippocampal image and % signal change graph with permission from Ref. [50\*\*]).

analyses of high-resolution fMRI were used to successfully classify similar indoor scenes in DG (but not entorhinal cortex) [42]. Thus, despite the highly overlapping input, the hippocampus produced stable differentiated (*i.e.* pattern-separated) representations. Potential evidence has also been provided for a lack of pattern separation for similar VR environments (similar shops in different locations; however the effects may also reflect inappropriate pattern completion) [43]. Finally, recent research has shown the extent of pattern separation for related events (scene-face pairs) predicts subsequent memory interference [44], linking pattern separation at encoding with reduced interference at retrieval. The studies provide critical evidence for pattern separation, for simple objects and more complex episodic events and spatial environments, in the human hippocampus.

Pattern completion refers to the retrieval of a complete distinct representation (or 'pattern') given a partial or ambiguous input. It is thought to underlie our ability to recollect prior events from minimal cues. For example, we might see a picture of a friend and recollect all the details of a social occasion with them from the previous week. Hippocampal subregion CA3, with its dense recurrent connections, is thought to act as an attractor network [45,46], underpinning pattern completion.

One way to assess pattern completion is to present participants with a single cue related to a complex event

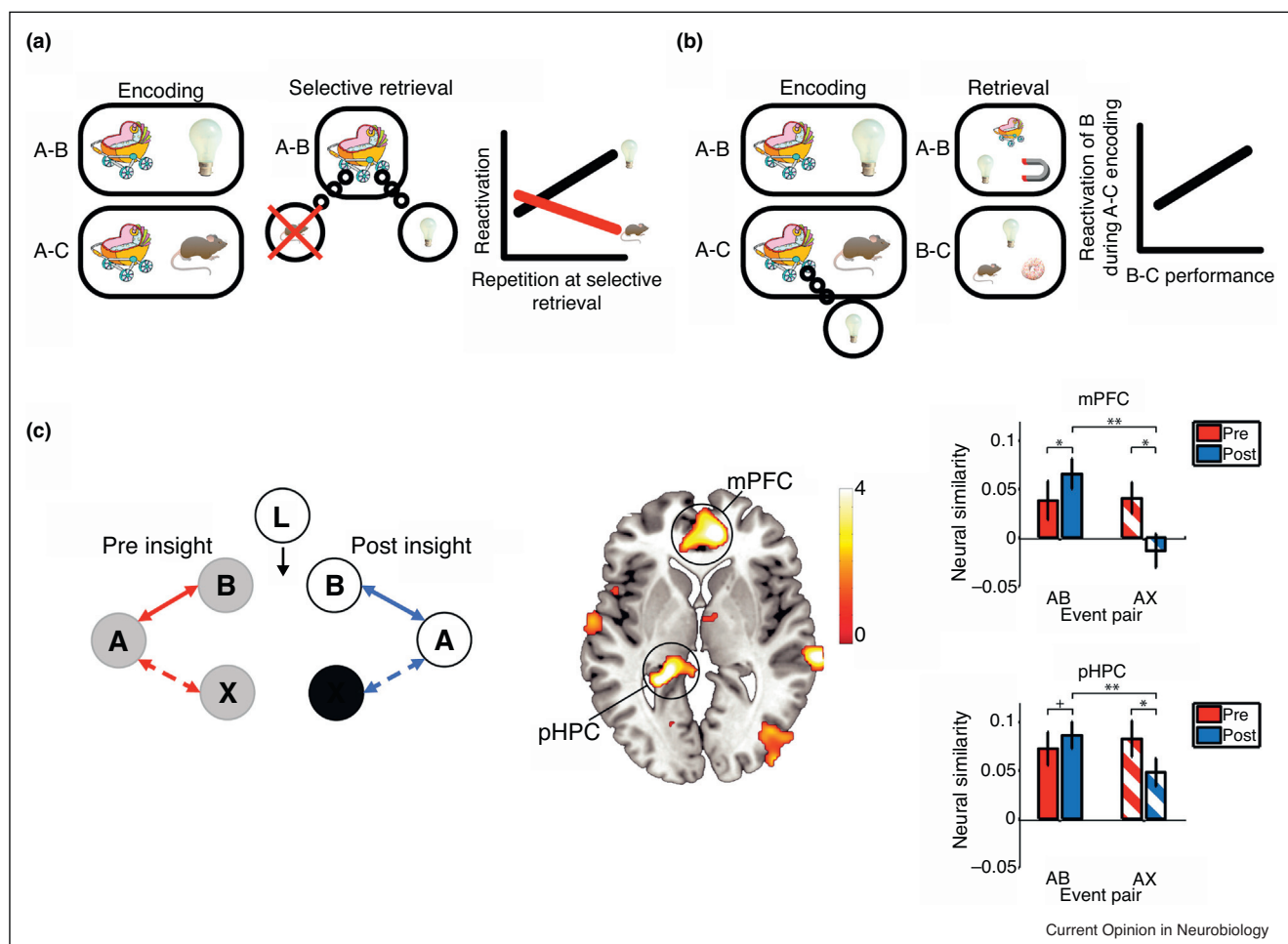
and assess whether all details of that event are subsequently retrieved. The presence of pattern completion predicts memory retrieval to be all-or-none, consistent with the 'recollection' component in dual process models of recognition memory [47]. Recent behavioural and fMRI evidence has been shown for this prediction. First, when complex events are learnt, for example location-person-object triplets, the retrieval success of elements within an event are related—if you retrieve one element correctly you are more likely to retrieve the other elements of the event successfully [48,49\*]. Using fMRI, it was shown that retrieval of these complex events was associated with a 'reinstatement' effect for all event elements in the neocortex, and that this reinstatement effect correlated with the hippocampal BOLD response [50\*\*] (Figure 2b). Cuing with the location leads to reinstatement of the person and object, and this reinstatement correlates with hippocampal activity. This is consistent with a pattern completion process in the hippocampus driving reinstatement of the complete event. However, the reinstatement effect was specific to the category (*e.g.* people vs. locations), but not the element of the event (*e.g.* Barack Obama vs. Hilary Clinton), and therefore could not distinguish between reinstatement of the correct vs. incorrect within-category element. Further, the authors were unable to distinguish between different hippocampal subfields, so were not able to conclude the hippocampal signal originated specifically from CA3.

More recently, evidence for attractor dynamics in relation to spatial environments has been provided [51<sup>\*</sup>]. Here, two distinct VR environments were learnt, and in a subsequent fMRI scanning phase, participants were placed in environments that morphed the surrounding landscape between the two learnt 'endpoint' environments. Consistent with rodent research [12], hippocampal representations for morphed environments showed a non-linear response where they became more similar to one of the endpoint representations across the trial, and this response predicted trial-by-trial mnemonic decision making. Thus, in the presence of an ambiguous cue, the

hippocampus pattern completes to one of the learnt environmental representations.

In sum, fMRI has shown the presence of both pattern separation and pattern completion in the human hippocampus. What is unclear is the relationship between these two computations. Typically, pattern separation is thought to occur at encoding and pattern completion at retrieval, however the distinction between encoding and retrieval is not clear in the real world. How do these two processes, and the two hippocampal subfields (DG and CA3), interact to maximise our ability to not just

Figure 3



Suppression, generalization and integration of pre-existing memories. **(a)** Evidence for suppression of associated material in the neocortex during selective retrieval was first provided by Wimber *et al.* Participants learn A-B, then A-C pairs. They are then cued with A and asked to selectively retrieve B (not C). During selective retrieval, neocortical patterns associated with B increased, while those associated with C decreased, suggesting the suppression of the competing associated item. Critically, the extent of neocortical suppression predicted later forgetting, suggesting that retrieval can adaptively shape our episodic memories of the past. **(b)** Evidence for integration following reactivation was first provided by Zeithamova *et al.* Participants first learnt A-B pairwise associations, followed by A-C pairs. Memory for A-B and A-C pairs was tested, as well as 'memory' for the non-encoded pairs (B-C). The extent of reactivation (measured by pattern classification of fMRI data) of item B when learning the A-C pairs correlated with performance for the non-encoded pairs. This suggests reactivation at encoding can result in the formation of novel associations between items never seen together (the B-C pairs). Examples shown in (a) and (b) are illustrative, and do not present actual stimuli used or data presented (see Refs. [57,56<sup>\*\*</sup>] for details). **(c)** Evidence that insight triggers the integration of separately learnt narrative structures in the hippocampus (and mPFC) was first shown by Milivojevic *et al.* Neural similarity (as measured with representational similarity analyses – RSA – of fMRI) between two separately learnt narratives (videos) increases after showing a 'linking' narrative (Section C with permission from Ref. [59<sup>\*</sup>]).

recall a previous event accurately, but also to apply our memories of the past to guide future behaviour? One possibility is that the hippocampus temporally segregates, but rapidly alternates between, pattern separation and completion, consistent with models proposing the segregation of encoding and retrieval within separate phases of the hippocampal theta rhythm [52<sup>\*</sup>].

This temporal segregation may also provide an answer to how a ‘Halle Berry’ and ‘Eiffel Tower’ neuron could maintain independent representations, whilst simultaneously maintaining a configural representation of the two elements. During specific phases of the theta rhythm, firing of hippocampal neurons will be primarily driven by neocortical input, and as such individual neurons will fire in relation to specific elements (*e.g.* Halle Berry). In other phases, firing will be driven by intra-hippocampal connections (*e.g.* recurrent connections in CA3), such that the ‘Halle Berry’ neuron will fire when presented with either Halle Berry or the Eiffel Tower.

### Post-encoding learning and plasticity

Our memories are as much about the future as the past. Ultimately, they must be behaviourally relevant to support decision-making processes. A new line of fMRI research has underlined how hippocampal representations are not static, but are malleable in nature—constantly being strengthened, weakened and altered in the presence of new information to ensure their continued behavioural relevance. The studies draw attention to the highly dynamic, plastic nature of representations in the hippocampus.

First, in an awake delay period between learning and test, endogenous reactivation of specific event memories was seen in entorhinal and retrosplenial cortex [53<sup>\*</sup>]. Importantly, the extent of reactivation correlated with subsequent memory performance. Thus, following initial encoding, memories are strengthened (or maintained) by a process of continuous reactivation in the MTL and neocortex. Interestingly, this endogenous reactivation also appears to facilitate learning of new overlapping material [54]. Memories can also be disrupted after encoding. When participants learn overlapping A-B and then A-C pairwise associations, the repeated retrieval of one pair (*e.g.* A-B) can result in poorer memory performance for the overlapping pair (*e.g.* A-C) [55]. Recent fMRI evidence shows that during retrieval of the A-B pair, the overlapping pair (A-C) is inhibited and the underlying representation is disrupted [56<sup>\*\*</sup>] (Figure 3a). Thus, memories can be strengthened or weakened after initial encoding dependent on the extent of post-encoding reactivation or suppression.

Event memories can also be altered and integrated with existing memories in order to generalise to novel situations. After learning an A-B pairwise association, the reactivation of element B (measured with fMRI) when

learning an overlapping A-C association correlates with participants’ subsequent performance on the non-encoded B-C pair [57] (Figure 3b). Further, the anterior hippocampus (and medial prefrontal cortex) appear to play a role in integrating representations for overlapping information [58<sup>\*</sup>]. Thus, reactivation of previously learnt information can lead to generalisation between previously unseen elements. The hippocampus also appears to play a crucial role in the integration of separately learnt narrative structures when participants become aware that they relate to a larger coherent narrative, resulting in an insight-triggered reconfiguration of memory space [59<sup>\*</sup>] (Figure 3c). Interestingly, these reconfigured narratives might be represented in a hierarchical manner along the long-axis of the hippocampus [60]. Related to this, the hippocampus also appears to represent the community structure of temporally related stimuli [61]. In sum, the representational space in the human hippocampus can be complex, structured and hierarchical, and most importantly, it is highly dynamic, constantly strengthening, weakening and altering existing representations to appropriately guide decision-making processes [62,63<sup>\*\*</sup>].

### Conclusion

Recent electrophysiology and functional brain imaging research has focused on the computations performed by the human hippocampus. In line with computational models, the human hippocampus appears to rapidly learn arbitrary associations between event elements, pattern separate overlapping neocortical input at encoding, and pattern complete partial neocortical input at retrieval. Thus, it is only recently that the mechanistic underpinnings of episodic and spatial memory in humans have been revealed. Further, research has suggested the hippocampus is involved in more than simply ‘remembering’. Rather, it supports a dynamic, plastic, flexible representational space that is continually altering and integrating memories of the past in order to guide decisions in the present [64,65].

### Conflict of interest statement

Nothing declared.

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### References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Scoville WB, Milner B: **Loss of recent memory after bilateral hippocampal lesions.** *J Neurol Neurosurg Psychiatry* 1957, **20**:11-21.
2. Lou Smith M, Milner B: **The role of the right hippocampus in the recall of spatial location.** *Neuropsychologia* 1981, **19**:781-793.
3. Mayes AR, Holdstock JS, Isaac CL, Montaldi D, Grigor J, Gummer A, Cariga P, Downes JJ, Tsivilis D, Gaffan D *et al.*: **Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition.** *Hippocampus* 2004, **14**:763-784.
4. Horner AJ, Gadian DG, Fuentemilla L, Jentschke S, Vargha-Khadem F, Duzel E: **A rapid, hippocampus-dependent, item-memory signal that initiates context memory in humans.** *Curr Biol* 2012, **22**:2369-2374.
5. Kumaran D, Hassabis D, Spiers HJ, Vann SD, Vargha-Khadem F, Maguire EA: **Impaired spatial and non-spatial configural learning in patients with hippocampal pathology.** *Neuropsychologia* 2007, **45**:2699-2711.
6. Ryan JD, Althoff RR, Whitlow S, Cohen NJ: **Amnesia is a deficit in relational memory.** *Psychol Sci* 2000, **11**:454-461.
7. Tulving E: *Elements of Episodic Memory*. Clarendon Press; 1983.
8. Marr D: **Simple memory: a theory for archicortex.** *Philos Trans R Soc London B* 1971, **262**:23-81.  
This paper laid the foundations for the computational account of how the hippocampus and neocortex support episodic memory.
9. McClelland JL, McNaughton BL, O'Reilly RC: **Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory.** *Psychol Rev* 1995, **102**:419-457.
10. Norman KA, O'Reilly RC: **Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach.** *Psychol Rev* 2003, **110**:611-646.
11. Rolls ET: **Functions of neuronal networks in the hippocampus and neocortex in memory.** In *Neural Models of Plasticity: Experimental and Theoretical Approaches*. Edited by Byrne JH, Berry WO. Academic Press; 1989:240-265.
12. Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J: **Attractor dynamics in the hippocampal representation of the local environment.** *Science* 2005, **308**:873-876.
13. Nakazawa K, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA *et al.*: **Requirement for hippocampal CA3 NMDA receptors in associative memory recall.** *Science* 2002, **297**:211-218.
14. Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser M-B: **Independent codes for spatial and episodic memory in hippocampal neuronal ensembles.** *Science* 2005, **309**:619-623.
15. Damasio AR: **The brain binds entities and events by multiregional activation from convergence zones.** *Neural Comput* 1989, **1**:123-132.
16. Backus AR, Bosch SE, Ekman M, Grabovsky AV: **Mnemonic convergence in the human hippocampus.** *Nat Commun* 2016, **7**:11991.  
Combining MVPA and graph-based connectivity analyses, this study provides evidence for a convergence zone in the hippocampus, characterized by conjunctive memory coding and hub-like network connectivity.
17. O'Keefe J, Dostrovsky J: **The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat.** *Brain Res* 1971, **34**:171-175.
18. Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham A, Newman EL, Fried I: **Cellular networks underlying human spatial navigation.** *Nature* 2003, **425**:184-188.
19. Jacobs J, Weidemann CT, Miller JF, Solway A, Burke JF, Wei X-X, Suthana N, Sperling MR, Sharan AD, Fried I *et al.*: **Direct recordings of grid-like neuronal activity in human spatial navigation.** *Nat Neurosci* 2013, **16**:1188-1191.
20. Miller JF, Fried I, Suthana N, Jacobs J: **Repeating spatial activations in human entorhinal cortex.** *Curr Biol* 2015, **25**:1080-1085.
21. Hassabis D, Chu C, Rees G, Weiskopf N, Molyneux PD, Maguire EA: **Decoding neuronal ensembles in the human hippocampus.** *Curr Biol* 2009, **19**:546-554.
22. Doeller CF, Barry C, Burgess N: **Evidence for grid cells in a human memory network.** *Nature* 2010, **463**:657-661.  
This fMRI study provided the first evidence for a grid-like signal in human entorhinal cortex and a wider cortical memory network during spatial navigation in a virtual reality environment.
23. Chadwick MJ, Jolly AEJ, Amos DP, Hassabis D, Spiers HJ: **A goal direction signal in the human entorhinal/subicular region.** *Curr Biol* 2015, **25**:87-92.
24. Vass LK, Epstein RA: **Abstract representations of location and facing direction in the human brain.** *J Neurosci* 2013, **33**:6133-6142.  
This fMRI study provided critical evidence for location-based and heading direction-based representations in the human brain.
25. Bonnici HM, Kumaran D, Chadwick MJ, Weiskopf N, Hassabis D, Maguire EA: **Decoding representations of scenes in the medial temporal lobes.** *Hippocampus* 2012, **22**:1143-1153.
26. Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I: **Invariant visual representation by single neurons in the human brain.** *Nature* 2005, **435**:1102-1107.  
This seminal single-unit electrophysiology study provided the first evidence for 'concept' cells in the human hippocampus.
27. Kreiman G, Koch C, Fried I: **Category-specific visual responses of single neurons in the human medial temporal lobe.** *Nat Neurosci* 2000, **3**:946-953.
28. Quiroga RQ, Kreiman G, Koch C, Fried I: **Sparse but not "grandmother-cell" coding in the medial temporal lobe.** *Trends Cogn Sci* 2008, **12**:87-91.
29. Bowers JS: **More on grandmother cells and the biological implausibility of PDP models of cognition: a reply to Plaut and McClelland (2010) and Quiroga and Kreiman (2010).** *Psychol Rev* 2010, **117**:300-306.
30. Plaut DC, McClelland JL: **Locating object knowledge in the brain: comment on Bowers's (2009) attempt to revive the grandmother cell hypothesis.** *Psychol Rev* 2010, **117**:284-288.
31. De Falco E, Ison MJ, Fried I, Quiroga R: **Long-term coding of personal and universal associations underlying the memory web in the human brain.** *Nat Commun* 2016, **7**:13408.
32. Quiroga RQ: **Concept cells: the building blocks of declarative memory functions.** *Nat Rev Neurosci* 2012, **13**:587-597.
33. Quiroga R, Kraskov A, Koch C, Fried I: **Explicit encoding of multimodal percepts by single neurons in the human brain.** *Curr Biol* 2009, **19**:1308-1313.
34. Monaco JD, Rao G, Roth ED, Knierim JJ: **Attentive scanning behavior drives one-trial potentiation of hippocampal place fields.** *Nat Neurosci* 2014, **17**:725-731.  
This fascinating electrophysiology study in rodents shows that hippocampal cell activity during exploratory head scanning predicted whether a place field emerged in subsequent trials, possibly reflecting a biological substrate of one-shot episodic memory formation.
35. Ison MJ, Quiroga R, Fried I: **Rapid encoding of new memories by individual neurons in the human brain.** *Neuron* 2015, **87**:220-230.  
The first clear demonstration that single cells in the human hippocampus provide a conjunctive code for the association of previously unrelated items.
36. Miller JF, Neufang M, Solway A, Brandt A, Trippel M, Mader I, Heft S, Merkow M, Polyn SM, Jacobs J *et al.*: **Neural activity in human hippocampal formation reveals the spatial context of retrieved memories.** *Science* 2013, **342**:1111-1114.
37. Bakker A, Kirwan CB, Miller M, Stark CEL: **Pattern separation in the human hippocampal CA3 and dentate gyrus.** *Science* 2008, **319**:1640-1642.  
This fMRI study provided the first evidence for a possible pattern separation signal in the human hippocampus.

38. Lacy JW, Yassa MA, Stark SM, Muftuler LT, Stark CEL: **Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity.** *Learn Mem* 2011, **18**:15-18.
39. Motley SE, Kirwan CB: **A parametric investigation of pattern separation processes in the medial temporal lobe.** *J Neurosci* 2012, **32**:13076-13084.
40. Kumaran D, Maguire EA: **Match-mismatch processes underlie human hippocampal responses to associative novelty.** *J Neurosci* 2007, **27**:8517-8524.
41. Chadwick MJ, Hassabis D, Maguire EA: **Decoding overlapping memories in the medial temporal lobes using high-resolution fMRI.** *Learn Mem* 2011, **8**:742-746.
42. Berron D, Schutze H, Maass A, Cardenas-blanco A, Kuijff HJ, Kumaran D, Duzel E: **Strong evidence for pattern separation in human dentate gyrus.** *J Neurosci* 2016, **36**:7569-7579.
43. Kyle CT, Stokes JD, Lieberman JS, Hassan AS, Ekstrom AD: **Successful retrieval of competing spatial environments in humans involves hippocampal pattern separation mechanisms.** *Elife* 2015, **4**:e10499.
44. Chanales AJH, Favila SE, Kuhl BA: **Experience-dependent hippocampal pattern differentiation prevents interference during subsequent learning.** *Nat Commun* 2016:11066.
45. Hopfield J: **Neural networks and physical systems with emergent collective computational abilities.** *Proc Natl Acad Sci U S A* 1982, **79**:2554-2558.
46. Treves A, Rolls ET: **Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network.** *Hippocampus* 1992, **2**:189-199.
47. Yonelinas AP: **Receiver-operating characteristics in recognition memory: evidence for a dual-process model.** *J Exp Psychol Learn Mem Cogn* 1994, **20**:1341-1354.
48. Horner AJ, Burgess N: **The associative structure of memory for multi-element events.** *J Exp Psychol Gen* 2013, **142**:1370-1383.
49. Horner AJ, Burgess N: **Pattern completion in multielement event engrams.** *Curr Biol* 2014, **24**:988-992.  
This behavioural and statistical modelling paper provided the first evidence for a possible behavioural signature of pattern completion for complex episodic events.
50. Horner AJ, Bisby JA, Bush D, Lin W-JW, Burgess N: **Evidence for holistic episodic recollection via hippocampal pattern completion.** *Nat Commun* 2015, **6**:1-11.  
Combining behaviour and fMRI in humans, and computational modelling, the study provides the first evidence for hippocampal pattern completion and neocortical reinstatement for complex multi-element events.
51. Steemers B, Vicente-grabovetsky A, Barry C, Smulders P, Burgess N, Doeller CF: **Hippocampal attractor dynamics predict memory-based decision making.** *Curr Biol* 2016, **26**:1750-1757.  
This fMRI used representational similarity analysis to provide evidence for attractor dynamics in the human hippocampus during virtual navigation.
52. Hasselmo ME, Aon CB, Wyble BP, Hasselmo ME, Aon CB, Wyble BP: **A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning.** *Neural Comput* 2002, **14**:793-817.  
This paper outlines a computational model of the hippocampus, hypothesising a role for theta oscillations in temporally segregating memory encoding and retrieval.
53. Staresina BP, Alink A, Kriegeskorte N, Henson RN: **Awake reactivation predicts memory in humans.** *Proc Natl Acad Sci U S A* 2013, **110**:21159-21164.  
This fMRI study used multivariate pattern analyses to show how reactivation of memory representations during awake 'offline' periods predicts subsequent memory performance in humans.
54. Schlichting ML, Preston AR: **Memory reactivation during rest supports upcoming learning of related content.** *Proc Natl Acad Sci U S A* 2014, **2014**:1-6.
55. Anderson MC, Bjork RA, Bjork EL: **Remembering causes forgetting: retrieval dynamics in long-term memory.** *J Exp Psychol Learn Mem Cogn* 1994, **20**:1063-1087.
56. Wimber M, Alink A, Charest I, Kriegeskorte N, Anderson MC: **Retrieval induces adaptive forgetting of competing memories via cortical pattern suppression.** *Nat Neurosci* 2015, **18**:582-589.  
This elegant fMRI study shows that neural representations of competing memories during retrieval can be suppressed in the neocortex, and that this neural mechanism relates to subsequent forgetting.
57. Zeithamova D, Dominick AL, Preston AR: **Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference.** *Neuron* 2012, **75**:168-179.
58. Schlichting ML, Mumford JA, Preston AR: **Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex.** *Nat Commun* 2015, **6**:1-10.  
This fMRI study used representational similarity analyses to demonstrate which regions of the human hippocampus and medial prefrontal cortex support memory separation and integration.
59. Milivojevic B, Vicente-Grabovetsky A, Doeller CF: **Insight reconfigures hippocampal-prefrontal memories.** *Curr Biol* 2015, **25**:821-830.  
This fMRI study used representational similarity analyses to show how mnemonic representations for narratives in the human hippocampus and medial prefrontal cortex change when relevant post-encoding information links previously separate narratives.
60. Collin SHP, Milivojevic B, Doeller CF: **Memory hierarchies map onto the hippocampal long axis in humans.** *Nat Neurosci* 2015, **18**:1562-1564.
61. Schapiro AC, Rogers TT, Cordova NI, Turk-browne NB, Botvinick MM: **Neural representations of events arise from temporal community structure.** *Nat Neurosci* 2013, **16**:486-492.
62. Wimmer GE, Shohamy D: **Preference by association: how memory mechanisms in the hippocampus bias decisions.** *Science* 2012, **338**:270-273.
63. Shadlen MN, Shohamy D: **Decision making and sequential sampling from memory.** *Neuron* 2016, **90**:927-939.  
This theoretical paper presents a framework for how memories can guide decisions, via a sequential sampling mechanism similar in nature to the mechanisms thought to underpin perceptual decision making.
64. McKenzie S, Eichenbaum H: **Consolidation and reconsolidation: two lives of memories?** *Neuron* 2011, **71**:224-233.
65. Dudai Y: **The restless engram: consolidations never end.** *Annu Rev Neurosci* 2012, **35**:227-247.
66. Hartley T, Lever C, Burgess N, O'Keefe J: **Space in the brain: how the hippocampal formation supports spatial cognition.** *Philos Trans R Soc B* 2014, **369**:20120510.