Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Memory allocation and integration in rodents and humans

Margaret L Schlichting[1] and Paul W Frankland[1,2,3,4]

In rodents, recent studies indicate that levels of neuronal excitability dictate which cell populations encode a memory for a particular event (i.e. memory allocation), and whether memories for multiple events become linked. In human subjects, imaging methods now allow for detection of brain responses to specific events, and therefore make it possible to address whether analogous processes are engaged. Similar to rodents, these studies reveal that neural engagement prior to learning influences encoding in humans. Furthermore, they provide evidence that events that share content, or occur close together in time, become linked during learning or during later 'offline' processing (i.e. memory integration). These concepts of memory allocation and memory integration provide a common mechanistic framework for considering how knowledge emerges in rodents and humans.

Addresses
[1] Department of Psychology, University of Toronto, Toronto, ON M5S 3G3, Canada
[2] Program in Neurosciences & Mental Health, Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada
[3] Department of Physiology, University of Toronto, Toronto, ON M5G 1X8, Canada
[4] Institute of Medical Sciences, University of Toronto, Toronto, ON M5S 1A8, Canada

Corresponding authors:
Schlichting, Margaret L (schlichting@psych.utoronto.ca),
Frankland, Paul W (paul.frankland@sickkids.ca)

Current Opinion in Behavioral Sciences 2017, **17**:90–98

This review comes from a themed issue on **Memory in time and space**

Edited by **Lila Davachi** and **Neil Burgess**

http://dx.doi.org/10.1016/j.cobeha.2017.07.013

Introduction

Richard Semon, the German evolutionary zoologist, introduced two enduring terms to the memory literature: 'engram' and 'ecphory'. An engram refers to the physical changes in brain state that are induced by an event (i.e. the memory trace). Once formed, an engram becomes dormant but may be awakened by presentation of the original (or similar) stimulus, in a process Semon defined as ecphory (i.e. memory retrieval) [1]. Following from Semon, three strategies have been used to provide evidence for the existence of engrams [2]. First, imaging and electrophysiological approaches have been used to detect persistent experience-dependent changes in neuronal morphology and/or activation (e.g. [3]). Second, lesion approaches have been used to ask whether removal of neural tissue containing the engram results in memory erasure (e.g. [4]). Third, stimulation approaches have been used to ask whether 'awakening' latent engrams leads to artificial memory expression in the absence of an external retrieval cue or internal retrieval attempt (e.g. [5]).

Many years on, the basic strategies used to detect and manipulate engrams remain the same, but technologies have improved dramatically. Today optogenetic and molecular approaches in mice allow active populations of neurons to be tagged (e.g. during encoding), and then later manipulated (e.g. activated or silenced during memory recall). The use of these tools has allowed modern-day engram hunters to establish that (1) populations of neurons engaged during encoding are reactivated during successful memory retrieval; (2) inhibition of these tagged populations of neurons prevents successful retrieval; and (3) activation of these populations of neurons results in artificial memory expression (in the absence of external retrieval cues) [2,6,7].

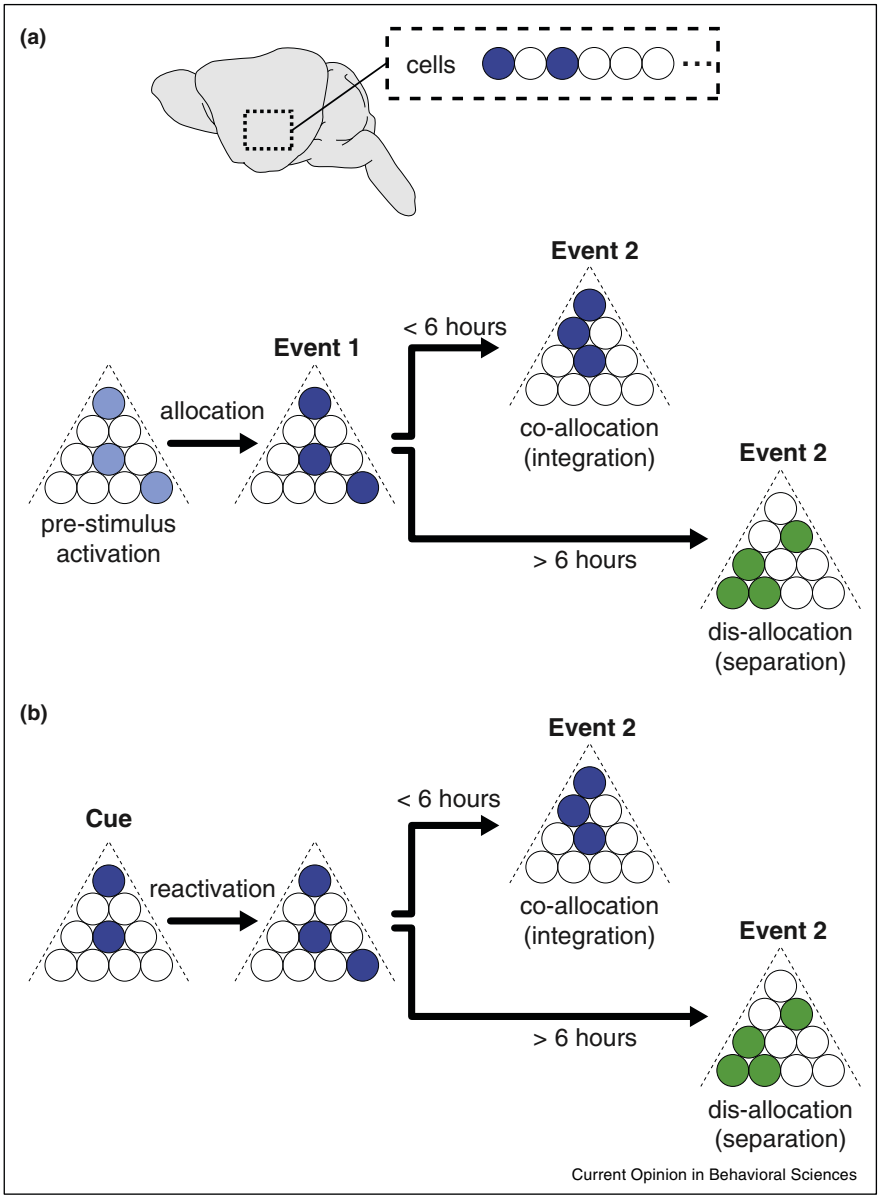
Against this backdrop, here we ask whether studies in humans provide analogous evidence for the existence of engrams. Recent advances in functional magnetic resonance imaging (fMRI) analysis [8] have made it possible to estimate the brain response evoked by specific events [9] or individual memory elements [10,11•], allowing engrams to be approximated in humans. In the first section, we focus on a single memory, and consider factors that influence how it is encoded, and how consolidation alters its organization and quality over time. In the second section, we consider how memories interact, and specifically focus on factors influencing the storage and transformation of complex memories integrated across multiple experiences.

Memory for a single episode

Allocation

Most researchers have considered the time of percept as the birth of a memory (e.g. [12]). However, recent studies have highlighted that neural engagement prior to an experience dictates how new information is encoded. In rodents, experimental manipulation of intrinsic

Figure 1



Allocation, co-allocation and dis-allocation in rodents. **(a)** In the lateral amygdala before an event occurs, a subpopulation of principal neurons is more excitable (light blue) than their neighbours (white). During event 1, this population of more excitable neurons becomes allocated to the engram underlying event 1 (dark blue). These allocated neurons remain transiently more excited following encoding of event 1. If a second event occurs within this window of excitability (<6 hours), then this same (or overlapping) population of neurons is allocated to the second event (dark blue) (co-allocation). If a second event occurs beyond this time window (>6 hours), then a non-overlapping population of neurons is allocated to the second event (green) (dis-allocation). **(b)** Following cue-induced recall of event 1, the allocated neurons are reactivated and remain transiently more excitable (dark blue) than their neighbours (white). If a second event occurs within this window of excitability (<6 hours), then this same (or overlapping) population of neurons is allocated to the second event (dark blue) (co-allocation). If a second event occurs beyond this time window (>6 hours), then a non-overlapping population of neurons is allocated to the second event (green) (dis-allocation).

excitability of lateral amygdala principal neurons influences whether those cells become part of a fear memory engram, with more excitable neurons 'capturing' the memory trace [13] (Figure 1). Subsequent deletion [14] or silencing [15••,16,17] of this population of neurons (and not a random, equivalently-sized population of neurons) prevents fear memory expression, indicating that these cells formed an essential component of the fear memory trace. This pattern is observed using a variety of methods to alter excitability (including expression of potassium channels, excitatory opsins and DREADDs), in other brain regions (including the hippocampus [18••,19] and

cortex [20]), and across a variety of tasks (including appetitively-motivated tasks [21]). Moreover, relative excitability levels influence allocation under more natural conditions (i.e. in situations where neuronal excitability is not explicitly manipulated prior to learning [22]), indicating that spontaneous fluctuations in excitability dictate how information is encoded.

In humans, neural engagement prior to learning similarly influences encoding. The majority of this work has been carried out at the trial-general level, showing that an optimal brain state may be engaged in preparation for encoding (e.g. with pre-stimulus medial temporal lobe [MTL] activation or theta oscillations predicting later memory [23–25]). Preparatory states may also impact memory formation on a longer timescale. One study showed that enhanced hippocampal–neocortical connectivity during pre-encoding sleep was associated with superior learning approximately 30 min later [26]. A possible account for this collection of findings is that the neural networks later used to encode the information via LTP are potentiated pre-encoding, perhaps through dopamine or norepinephrine release [27]. However, because these analyses are carried out by averaging across multiple trials in an experiment, inferences cannot be made about neuronal allocation for individual memories; thus, how this research relates to the rodent work isolating specific memory engrams remains to be seen.

Offline processing

Once a memory has been encoded, the hippocampus is thought to drive reinstatement of declarative memories in neocortical regions during offline periods [28,29]. Signs of early phase consolidation can be detected in humans immediately following learning: After encoding, enhanced hippocampal connectivity during both periods of passive rest [30–32] and unrelated tasks [33] predict later memory. The hippocampal activation patterns evoked during rest are similar to those elicited during the original encoding experience, suggesting reinstatement of encoded information during post-learning periods [34] — perhaps analogous to replay phenomena in rodents. Several reports have linked increased post-encoding processing to better memory after a long delay (e.g. 24 hours) [30,33,35], suggesting that processes engaged in the immediate post-encoding period of (awake) rest support mnemonic durability [28]. Many learning repetitions may also speed the formation of stable neocortical representations [36], perhaps performing a function similar to that of offline reactivations.

The bulk of memory consolidation occurs over longer periods of time, spanning months to years in adult humans (perhaps occurring more quickly in children [37]) and naturally including periods of sleep. A host of recent work has highlighted the importance of slow-wave sleep (SWS) in stabilizing declarative memory traces (beginning in infancy [38]), with more SWS-related signatures predicting better memory outcomes [39]. One series of studies shows that reactivating memories during SWS — but not during awake rest [40] (but see [41]) or rapid eye movement (REM) sleep [42] — specifically strengthens those memories that were reactivated, as probed by a subsequent memory test [43]. Sleep may also serve to unbind event memories from the specific context in which they were experienced, with sleep leading to enhanced transfer of learned information to a new spatial context in rodents [44] (but see [45]). This decontextualizing function of sleep may, in part, account for the oft-observed phenomenon in humans that (recollection-based) memory for experiential details decays faster than (familiarity-based) memory for general gist [46,47], leading to semanticization of memories over time [48•].

In addition to a qualitative change in the kind of information recalled, memory consolidation is associated with changes in memory organization. Memories for new events may initially engage hippocampus, but, with time, become increasingly dependent on neocortical circuits [49]. Recent studies in rodents suggest that neurons in the prefrontal cortex (PFC) are allocated at the time of initial learning, even though they do not functionally contribute to memory expression until days or weeks later [50,51].

Similarly, human fMRI studies have also shown that different neural networks are engaged for retrieval of recent versus remote memories. While retrieval of recently encoded information engages primarily MTL regions, more remote memories additionally activate neocortical regions such as ventromedial PFC [39] and anterior temporal lobe [52,53]. Investigations specifically differentiating between anterior and posterior hippocampus further suggest that while posterior hippocampal response declines relatively rapidly (as quickly as 48 hours [54]), engagement of anterior hippocampus is more stable [52] (although perhaps differing across subfields within anterior hippocampus [55]). Collectively, these findings may be accounted for by recent proposals [56,57] that anterior and posterior hippocampus store gist-based and detail memories, respectively, with the amount of detail retrieval and posterior hippocampal involvement concomitantly decreasing, on average, as memories become more remote (however, retrieval of detailed, remote memories may still require hippocampus [58]).

Integrating memories of multiple episodes

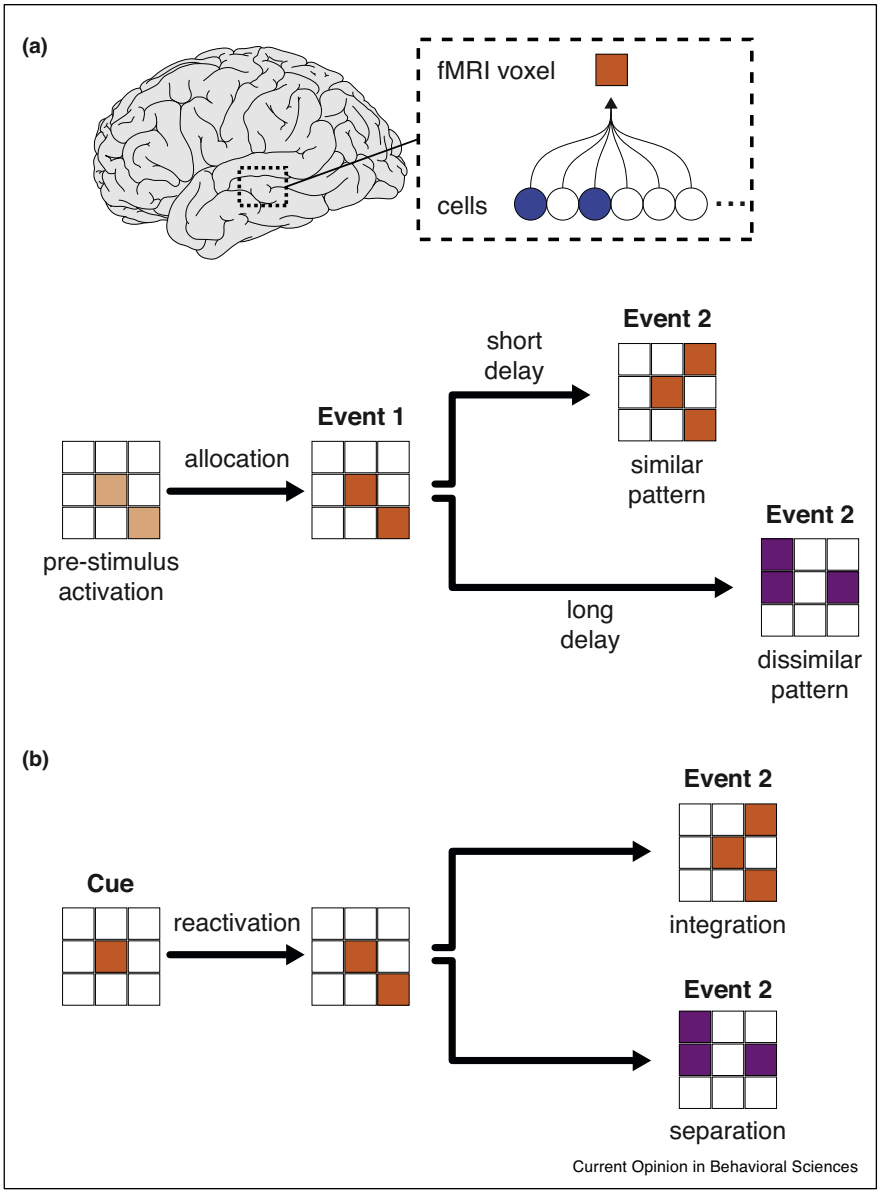
Individual memories rarely persist unchanged for a lifetime. Rather, we will later encounter new, related information that will trigger retrieval and modification — through updating, deletion (see however [59]), or distortion — of an existing memory. This idea is echoed across the literature in a number of phenomena,

including reconsolidation [60], memory integration [61], and retrieval-mediated learning [62]. Here, we focus on memory integration, in which memories for separate but related experiences become linked (Figure 2).

Linking memories

While it is known that pre-encoding excitability influences allocation in animals, less work has been done to investigate this phenomenon in humans. Do the

Figure 2



Theoretical allocation, integration, and separation signatures as measured in the human brain. **(a)** Activation of a single fMRI voxel (square) represents the average response across a population of neurons (circles; also as in Figure 1). Voxels active (light orange) relative to an arbitrary baseline (white) just prior to an Event 1 are more likely to be recruited as part of the neural representation of that event (dark orange). Subsequent events (i.e. Event 2) presented after a short (top arrow) or long (bottom arrow) delay may evoke similar (dark orange) and dissimilar (purple) activation patterns, respectively. Naturally occurring fluctuations in neural response may thus yield more similar neural representations (measured as the correlation between Event 1 and Event 2 patterns) for events experienced close in time. **(b)** A similar mechanism can support memory integration across events related by shared content. The familiar elements in an Event 2 serve as a retrieval cue, leading to reactivation of the Event 1 representation. Event 2 may then be encoded in an overlapping (integrated; top arrow, orange pattern) or non-overlapping (separated; bottom arrow, purple pattern) neural representation. Both reactivation and integration/separation steps may be influenced by a number of factors in humans, including delay, memory strength, schema, goals, and awareness.

particular neurons engaged prior to event onset preferentially become a part of the engram? If so, this would be one mechanism by which memories for events that occur in immediate succession become linked, or integrated: Neurons active during an experience 1 would remain active during a closely following experience 2, yielding similar engrams for the two events [63,64]. Behaviourally, it is known that words learned close together within a list (i.e. in a similar temporal context) are often recalled together [65], consistent with the notion that back-to-back events may recruit overlapping neuronal populations. This idea has been tested in the human brain by comparing the fMRI responses evoked by specific encoding events: Recent studies have used trial-level analytic approaches [8] to show that hippocampal activation patterns are similar for items experienced adjacent in time [10] and support behavioural judgments of temporal closeness [66]. Taken together, these results are consistent with rodent work suggesting that excitability levels in the moments prior to encoding impact engram formation. (Note, however, that this question is practically quite difficult to ask directly in humans.)

It may also be advantageous at times to link memories for events experienced on different occasions that share, for instance, similar content. When a new episode is related to a prior experience, there are (at least) two possibilities for how the new information can be encoded: the old memory may be modified and linked to the new information through its allocation to overlapping neural populations (hereafter, integration); or, the new information may be encoded in a distinct trace (separation).[a] Integration and separation of related memories have been observed in anterior and posterior hippocampus, respectively [11•,69] (but see [70]). Mechanistically, integration occurs when previously stored memories are reactivated as new, related information is being encoded via hippocampal-medial prefrontal [61] theta oscillations [71], with MPFC guiding reinstatement of relevant memories [72] and driving mismatch computations [73]. Following retrieval, there is a time-limited window during which memories can be modified [74]. Mismatch between new events and prior memories triggers integration, with the resulting trace supporting a host of novel behaviours [61].

Box 1 Memory schema

A phenomenon closely related memory integration is the incorporation of new information into strong pre-existing knowledge structures, such as memory schema or semantic networks. In contrast to simple list-learning or associative learning tasks — which engage MTL regions to support new memory formation and updating, schema-based paradigms relying on pre-experimental knowledge or associative structures created across many learning repetitions [48•,94,95] may depend primarily on neocortical structures [96,97], especially medial PFC [98,99]. Such studies highlight the possibility that new information can be directly incorporated into existing knowledge stored across neocortex [100]. Recent work has shown that under these circumstances, novel information can rapidly become behaviourally [101] and neurally [102,103] indistinguishable from prior knowledge. For example, under certain learning conditions (e.g. so-called 'fast mapping'), integration of new words into the lexicon occurs almost immediately and persists into the next day [101]. Neural markers of consolidation emerge sooner when information can be linked to an existing schema [48•,94,95] suggesting that its consolidation may also be speeded, perhaps due to having a 'head start' in its transfer to neocortex.

From a theoretical perspective, reactivation of related memories is a necessary (but not sufficient [70,75]) condition of integration. Experimentally manipulating reactivation during, or just prior to, learning — such as by ordering experiences in a specific way (blocked versus intermixed [11•]) or by introducing a reminder cue [76,77] — influences both neural coding and behaviour, with integration preferentially observed during reactivation [78]. Reactivation and integration may also be more likely in the context of strong pre-existing knowledge (e.g. schema; Box 1) or when experimental conditions favor an intentional integration strategy (Box 2).

One factor that may impact integration is the temporal proximity at which the related events are experienced, with more proximal experiences being more likely allocated to overlapping neuronal populations. As discussed above, memories for two back-to-back experiences may have similar neural representations due to natural fluctuations in excitability. However, a similar outcome may also occur on a slightly longer timescale, in which temporally

Box 2 The role of goals and awareness

A number of studies highlight that cognitive factors such as the participant's goals [75] and awareness of the task structure [104] can influence the likelihood of integration. One experiment [75] manipulated participants' goals on a trial-by-trial basis while they were learning new information related to previously stored memories. Integration and retrieval goal states were neurally distinct, demonstrating that retrieval does not always lead to integration; the ultimate result of retrieval can be modulated by intentional strategy. Awareness of the task structure may also promote integration mechanisms [104], perhaps by boosting the likelihood of reactivation [61] or encouraging an explicit integration strategy [75]. However, several studies have shown that awareness is not necessary for integration to occur [105–108].

[a] Although we focus here on integration, separation or differentiation of related, 'confusable' memories is another critically important function of the hippocampus. In particular, recent fMRI work suggests that neural differentiation supports behaviour on tasks requiring individuation of specific memories (i.e., when discrimination demands are high [67,68]). Whether such separation signatures stem primarily from posterior hippocampal response, as would be predicted in the framework we describe here, remains unknown. Future work explicitly distinguishing anterior from posterior hippocampus and/or adopting a searchlight approach is needed to further elucidate the relationship between neural coding strategies and different levels of behavioural differentiation or abstraction.

separate (but related) experiences are integrated to the benefit of flexible behaviours. Rodent work has directly demonstrated that co-allocation is more likely for events closer together in time: experiences within hours (but not days) of each other are encoded by overlapping populations of neurons and show behavioural evidence of linkage [15••,18••]. Furthermore, memory retrieval appears to open up another opportunity for memory linking in rodents: When a second event (experience 2) closely follows retrieval for a previous event (experience 1) co-allocation is more likely [15••], and this may represent a mechanism for relating experiences by content.

Converging findings have been reported in humans, with greater neural and behavioural evidence for integration when related memories are encoded on the same versus different days [79••] and when initial memories are spontaneously reactivated during a rest period prior to learning [80]. Similar content (e.g. blocks of faces) preceding two otherwise unrelated events can also promote integration; behaviourally, doing so makes the events more likely to later be recalled together, especially when, according to a pattern classifier [81], the preceding content (i.e. face information) 'lingers' in the neural representations of both events ([82]; see also [83]). These findings suggest that a number of complex factors, including temporal proximity and content overlap, influence how the brain combines across multiple events to provide structure to memory allocation in neural — and thus, psychological — space.

Offline processing and knowledge generation

Much like memories for individual events, offline processing of integrated memories begins in the moments just after learning. Integration-specific enhancements in hippocampal–MPFC connectivity have been observed during awake rest immediately following encoding [84,85]. On a longer timescale, consolidation is thought to promote the extraction of regularities across multiple related memories [54] to be ultimately be stored in medial PFC [53,86]. Such extended consolidation periods allow rodents to form more general (or Gestalt) memories that average multiple instances [87] and depend on partial forgetting of details [88].

The specific sleep-based mechanisms that promote regularity extraction remain a topic of active research, with studies alternately implicating REM [89–91] and non-REM [92,93] sleep in integration. For instance, one study related sleep spindles during SWS to both better memory and less hippocampal response specifically for information related to existing memories [93]; spindles during post-learning naps may also support the generalization of learned words to novel category exemplars as early as in infancy [92]. On the other hand, a number of studies have shown that REM predicts post-sleep integration behaviour, including a superior ability to make decisions spanning related associations [89] and better memory for schema-congruent content [90].

While the specific sleep-based mechanisms are as yet unclear, sleep undoubtedly plays a critical role in the transformation of integrated memories. Regularity extraction over sleep may give rise to the increasingly gist-like quality of integrated memories over time, with idiosyncrasies removed to highlight generalizations across related episodes. On a larger scale, this mechanism may serve as the basis of general knowledge formation, with the gist-like nature and earlier reliance on neocortical structures making integrated memories more robust to forgetting.

Conclusions

In this review, we have considered how information is encoded and integrated in the brain. We review evidence that analogous processes are engaged in rodents and humans, and, in doing so, develop a common mechanistic framework for considering how knowledge emerges in rodents and humans.

Conflict of interest statement

Nothing declared.

Acknowledgements

We thank Michael Mack and Sheena Josselyn for helpful discussions and feedback on earlier drafts of this manuscript. This work was supported by a Canadian Institutes of Health Research grant to PWF (FDN143227).

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. Josselyn SA, Kohler S, Frankland PW: **Heroes of the engram**. *J Neurosci* 2017, **37**:4647-4657.
2. Josselyn SA, Kohler S, Frankland PW: **Finding the engram**. *Nat Rev Neurosci* 2015, **16**:521-534.
3. Wilson MA, McNaughton BL: **Reactivation of hippocampal ensemble memories during sleep**. *Science* 1994, **265**:676-679.
4. Lashley KS: **Integrative functions of the cerebral cortex**. *Physiol Rev* 1933, **13**:1-42.
5. Penfield W: **Engrams in the human brain. Mechanisms of memory**. *Proc R Soc Med* 1968, **61**:831-840.
6. Eichenbaum H: **Still searching for the engram**. *Learn Behav* 2016, **44**:209-222.
7. Tonegawa S *et al.*: **Memory engram cells have come of age**. *Neuron* 2015, **87**:918-931.
8. Kriegeskorte N, Mur M, Bandettini P: **Representational similarity analysis – connecting the branches of systems neuroscience**. *Front Syst Neurosci* 2008, **2**:4.
9. Xue G *et al.*: **Greater neural pattern similarity across repetitions is associated with better memory**. *Science* 2010, **330**:97-101.
10. Schapiro AC, Kustner LV, Turk-Browne NB: **Shaping of object representations in the human medial temporal lobe based on temporal regularities**. *Curr Biol* 2012, **22**:1622-1627.
11. • 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**:8151.
Schlichting and colleagues combine high-resolution fMRI with representational similarity analysis to ask whether items experienced as part of related associations develop more or less similar neural representations as a function of learning — indices of integration and separation, respectively. They also investigate whether codes are impacted by the ordering of experiences, presenting associations in a blocked or intermixed manner. The authors find that codes vary as a function of both training order and brain region: For instance, anterior hippocampus shows integration for associations learned in a blocked manner, while posterior hippocampus shows separation for both training schedules. These findings demonstrate that complementary representations exist in the human brain immediately following the encoding of overlapping experiences.

12. Dudai Y: **Time to remember**. *Neuron* 1997, **18**:179-182.

13. Han JH *et al.*: **Neuronal competition and selection during memory formation**. *Science* 2007, **316**:457-460.

14. Han JH *et al.*: **Selective erasure of a fear memory**. *Science* 2009, **323**:1492-1496.

15. •• Rashid AJ *et al.*: **Competition between engrams influences fear memory formation and recall**. *Science* 2016, **353**:383-387.
This study establishes that fear memories are more likely to be allocated to more excitable neurons in the lateral amygdala. Furthermore, they find that after encoding a memory, these 'engram' cells remain active for a few hours before their excitability levels fall back in line with their neighbours. They show that if a second event occurs within this window (i.e. $<$6 hours), then the memory for that event is encoded in exactly the same collection of neurons as the first memory (i.e. these memories become linked). In contrast, if the second event occurs outside of this window when the initial 'engram' cells are more active (i.e. a day later) then the memory for that second event is encoded in a different population of cells (i.e. these memories are separated). See also the Cai *et al*. [18••] paper.

16. Yiu AP *et al.*: **Neurons are recruited to a memory trace based on relative neuronal excitability immediately before training**. *Neuron* 2014, **83**:722-735.

17. Zhou Y *et al.*: **CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala**. *Nat Neurosci* 2009, **12**:1438-1443.

18. •• Cai DJ *et al.*: **A shared neural ensemble links distinct contextual memories encoded close in time**. *Nature* 2016, **534**:115-118.
Together with the Rashid *et al.* [15••] paper, this study establishes (1) that more excitable neurons are more likely to be allocated to an engram, and (2) excitability as a mechanism for linking memories for events that occur close together in time. In this paper, these principles are developed for place memories that engage the hippocampus.

19. Park S *et al.*: **Neuronal allocation to a hippocampal engram**. *Neuropsychopharmacology* 2016, **41**:2987-2993.

20. Choi GB *et al.*: **Driving opposing behaviors with ensembles of piriform neurons**. *Cell* 2011, **146**:1004-1015.

21. Hsiang HL *et al.*: **Manipulating a "cocaine engram" in mice**. *J Neurosci* 2014, **34**:14115-14127.

22. Gouty-Colomer LA *et al.*: **Arc expression identifies the lateral amygdala fear memory trace**. *Mol Psychiatry* 2016, **21**:1153.

23. Guderian S *et al.*: **Medial temporal theta state before an event predicts episodic encoding success in humans**. *Proc Natl Acad Sci U S A* 2009, **106**:5365-5370.

24. Park H, Rugg MD: **Prestimulus hippocampal activity predicts later recollection**. *Hippocampus* 2010, **20**:24-28.

25. Yoo JJ *et al.*: **When the brain is prepared to learn: enhancing human learning using real-time fMRI**. *Neuroimage* 2012, **59**:846-852.

26. van Dongen EV *et al.*: **Functional connectivity during light sleep is correlated with memory performance for face-location associations**. *Neuroimage* 2011, **57**:262-270.

27. Cohen N *et al.*: **Peri-encoding predictors of memory encoding and consolidation**. *Neurosci Biobehav Rev* 2015, **50**:128-142.

28. Carr MF, Jadhav SP, Frank LM: **Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval**. *Nat Neurosci* 2011, **14**:147-153.

29. Diekelmann S, Born J: **The memory function of sleep**. *Nat Rev Neurosci* 2010, **11**:114-126.

30. de Voogd LD, Fernandez G, Hermans EJ: **Awake reactivation of emotional memory traces through hippocampal–neocortical interactions**. *Neuroimage* 2016, **134**:563-572.

31. Staresina BP *et al.*: **Awake reactivation predicts memory in humans**. *Proc Natl Acad Sci U S A* 2013, **110**:21159-21164.

32. Tambini A, Ketz N, Davachi L: **Enhanced brain correlations during rest are related to memory for recent experiences**. *Neuron* 2010, **65**:280-290.

33. Tompary A, Duncan K, Davachi L: **Consolidation of associative and item memory is related to post-encoding functional connectivity between the ventral tegmental area and different medial temporal lobe subregions during an unrelated task**. *J Neurosci* 2015, **35**:7326-7331.

34. Tambini A, Davachi L: **Persistence of hippocampal multivoxel patterns into postencoding rest is related to memory**. *Proc Natl Acad Sci U S A* 2013, **110**:19591-19596.

35. Hermans EJ *et al.*: **Persistence of amygdala–hippocampal connectivity and multi-voxel correlation structures during awake rest after fear learning predicts long-term expression of fear**. *Cereb Cortex* 2016, **27**:3028-3041.

36. Brodt S *et al.*: **Rapid and independent memory formation in the parietal cortex**. *Proc Natl Acad Sci U S A* 2016, **113**:13251-13256.

37. Urbain C *et al.*: **Sleep in children triggers rapid reorganization of memory-related brain processes**. *Neuroimage* 2016, **134**:213-222.

38. Seehagen S *et al.*: **Timely sleep facilitates declarative memory consolidation in infants**. *Proc Natl Acad Sci U S A* 2015, **112**:1625-1629.

39. Takashima A *et al.*: **Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study**. *Proc Natl Acad Sci U S A* 2006, **103**:756-761.

40. Schreiner T, Goldi M, Rasch B: **Cueing vocabulary during sleep increases theta activity during later recognition testing**. *Psychophysiology* 2015, **52**:1538-1543.

41. Oudiette D *et al.*: **The role of memory reactivation during wakefulness and sleep in determining which memories endure**. *J Neurosci* 2013, **33**:6672-6678.

42. Cordi MJ *et al.*: **No effect of odor-induced memory reactivation during REM sleep on declarative memory stability**. *Front Syst Neurosci* 2014, **8**:157.

43. Creery JD *et al.*: **Targeted memory reactivation during sleep depends on prior learning**. *Sleep* 2015, **38**:755-763.

44. Borquez M *et al.*: **Sleep enhances inhibitory behavioral control in discrimination learning in rats**. *Exp Brain Res* 2014, **232**:1469-1477.

45. Jurewicz K *et al.*: **No evidence for memory decontextualization across one night of sleep**. *Front Hum Neurosci* 2016, **10**:7.

46. Ritchey M *et al.*: **Delay-dependent contributions of medial temporal lobe regions to episodic memory retrieval**. *Elife* 2015, **4**.

47. Talamini LM, Gorree E: **Aging memories: differential decay of episodic memory components**. *Learn Mem* 2012, **19**:239-246.

48. • Sommer T: **The emergence of knowledge and how it supports the memory for novel related information**. *Cereb Cortex* 2016, **28**:1906-1921.
This fMRI study followed participants longitudinally across 302 days as they learned and consolidated new object-location associative structures, or schemas. Sommer found behavioural and neural evidence consistent with 'semanticization' over the course of the experiment: a subjective shift in the quality of memories from 'remembering' to 'knowing' the initial associative encoding episode; as well as a decrease in hippocampal and increase in lateral PFC response during memory retrieval. These effects were mapped out across seven MRI sessions across the nearly year-long experiment, making this study the most comprehensive investigation of memory schema in humans to date.

49. Frankland PW, Bontempi B: **The organization of recent and remote memories**. *Nat Rev Neurosci* 2005, **6**:119-130.

50. Kitamura T *et al.*: **Engrams and circuits crucial for systems consolidation of a memory**. *Science* 2017, **356**:73-78.

51. Lesburgueres E *et al.*: **Early tagging of cortical networks is required for the formation of enduring associative memory**. *Science* 2011, **331**:924-928.

52. Bonnici HM *et al.*: **Detecting representations of recent and remote autobiographical memories in vmPFC and hippocampus**. *J Neurosci* 2012, **32**:16982-16991.

53. Nieuwenhuis IL, Takashima A: **The role of the ventromedial prefrontal cortex in memory consolidation**. *Behav Brain Res* 2011, **218**:325-334.

54. Sweegers CC *et al.*: **Neural mechanisms supporting the extraction of general knowledge across episodic memories**. *Neuroimage* 2014, **87**:138-146.

55. Zeidman P, Lutti A, Maguire EA: **Investigating the functions of subregions within anterior hippocampus**. *Cortex* 2015, **73**:240-256.

56. Poppenk J *et al.*: **Long-axis specialization of the human hippocampus**. *Trends Cogn Sci* 2013, **17**:230-240.

57. Strange BA *et al.*: **Functional organization of the hippocampal longitudinal axis**. *Nat Rev Neurosci* 2014, **15**:655-669.

58. Wiltgen BJ *et al.*: **The hippocampus plays a selective role in the retrieval of detailed contextual memories**. *Curr Biol* 2010, **20**:1336-1344.

59. Gisquet-Verrier P *et al.*: **Integration of new information with active memory accounts for retrograde amnesia: a challenge to the consolidation/reconsolidation hypothesis?** *J Neurosci* 2015, **35**:11623-11633.

60. Nader K, Einarsson EO: **Memory reconsolidation: an update**. *Ann N Y Acad Sci* 2010, **1191**:27-41.

61. Schlichting ML, Preston AR: **Memory integration: neural mechanisms and implications for behavior**. *Curr Opin Behav Sci* 2015, **1**:1-8.

62. Iordanova MD, Good M, Honey RC: **Retrieval-mediated learning involving episodes requires synaptic plasticity in the hippocampus**. *J Neurosci* 2011, **31**:7156-7162.

63. Frankland PW, Josselyn SA: **Memory allocation**. *Neuropsychopharmacology* 2015, **40**:243.

64. Silva AJ *et al.*: **Molecular and cellular approaches to memory allocation in neural circuits**. *Science* 2009, **326**:391-395.

65. Howard MW, Kahana MJ: **A distributed representation of temporal context**. *J Math Psychol* 2002, **46**:269-299.

66. Ezzyat Y, Davachi L: **Similarity breeds proximity: pattern similarity within and across contexts is related to later mnemonic judgments of temporal proximity**. *Neuron* 2014, **81**:1179-1189.

67. Favila SE, Chanales AJ, Kuhl BA: **Experience-dependent hippocampal pattern differentiation prevents interference during subsequent learning**. *Nat Commun* 2016, **7**:11066.

68. Hulbert JC, Norman KA: **Neural differentiation tracks improved recall of competing memories following interleaved study and retrieval practice**. *Cereb Cortex* 2015, **25**:3994-4008.

69. Collin SH, Milivojevic B, Doeller CF: **Memory hierarchies map onto the hippocampal long axis in humans**. *Nat Neurosci* 2015, **18**:1562-1564.

70. Kim G, Norman KA, Turk-Browne NB: **Neural differentiation of incorrectly predicted memories**. *J Neurosci* 2017, **37**:2022-2031.

71. Sans-Dublanc A *et al.*: **Distinct neurophysiological mechanisms support the online formation of individual and across-episode memory representations**. *Cereb Cortex* 2016. [Epub ahead of print].

72. Place R *et al.*: **Bidirectional prefrontal–hippocampal interactions support context-guided memory**. *Nat Neurosci* 2016, **19**:992-994.

73. Garrido MI *et al.*: **Ventromedial prefrontal cortex drives hippocampal theta oscillations induced by mismatch computations**. *Neuroimage* 2015, **120**:362-370.

74. de Beukelaar TT *et al.*: **Reconsolidation of motor memories is a time-dependent process**. *Front Hum Neurosci* 2016, **10**:408.

75. Richter FR, Chanales AJ, Kuhl BA: **Predicting the integration of overlapping memories by decoding mnemonic processing states during learning**. *Neuroimage* 2016, **124(Pt A)**:323-335.

76. Gershman SJ *et al.*: **Neural context reinstatement predicts memory misattribution**. *J Neurosci* 2013, **33**:8590-8595.

77. Hupbach A *et al.*: **Reconsolidation of episodic memories: a subtle reminder triggers integration of new information**. *Learn Mem* 2007, **14**:47-53.

78. St Jacques PL, Olm C, Schacter DL: **Neural mechanisms of reactivation-induced updating that enhance and distort memory**. *Proc Natl Acad Sci U S A* 2013, **110**:19671-19678.

79. •• Zeithamova D, Preston AR: **Temporal proximity promotes integrtaion of overlapping events**. *J Cogn Neurosci* 2017, **29**:1311-1323.

Human participants encoded a series of related associations separated by either a 24-hour or 30-min delay. Behaviourally, participants were better at making inference judgments that spanned the related associations learned at a 30-min delay, consistent with integration of information learned close in time. Using a pattern classifier to decode the fMRI data, Zeithamova and Preston also found that evidence for reactivation of prior memories was equivalent across 24-hour and 30-min delay conditions. However, using a classifier trained to identify activation patterns associated with integration on a separate group of participants, the authors found that neural evidence for integration was greater for the pairs learned at a 30-min delay. These results complement recent work in rodents [18••,15••] showing preferential integration of information learned within the same day.

80. Schlichting ML, Preston AR: **Memory reactivation during rest supports upcoming learning of related content**. *Proc Natl Acad Sci U S A* 2014, **111**:15845-15850.

81. Norman KA *et al.*: **Beyond mind-reading: multi-voxel pattern analysis of fMRI data**. *Trends Cogn Sci* 2006, **10**:424-430.

82. Chan SC *et al.*: **Lingering representations of stimuli influence recall organization**. *Neuropsychologia* 2017, **97**:72-82.

83. Morton NW, Polyn SM: **Beta-band activity represents the recent past during episodic encoding**. *Neuroimage* 2017, **147**:692-702.

84. Schlichting ML, Preston AR: **Hippocampal-medial prefrontal circuit supports memory updating during learning and post-encoding rest**. *Neurobiol Learn Mem* 2016, **134(Pt A)**:91-106.

85. van Kesteren MT *et al.*: **Persistent schema-dependent hippocampal–neocortical connectivity during memory encoding and postencoding rest in humans**. *Proc Natl Acad Sci U S A* 2010, **107**:7550-7555.

86. Lewis PA, Durrant SJ: **Overlapping memory replay during sleep builds cognitive schemata**. *Trends Cogn Sci* 2011, **15**:343-351.

87. Richards BA *et al.*: **Patterns across multiple memories are identified over time**. *Nat Neurosci* 2014, **17**:981-986.

88. Richards BA, Frankland PW: **The persistence and transience of memory**. *Neuron* 2017, **94**:1071-1084.

89. Alger SE, Payne JD: **The differential effects of emotional salience on direct associative and relational memory during a nap**. *Cogn Affect Behav Neurosci* 2016, **16**:1150-1163.

90. Durrant SJ *et al.*: **Schema-conformant memories are preferentially consolidated during REM sleep**. *Neurobiol Learn Mem* 2015, **122**:41-50.

91. Sterpenich V *et al.*: **Memory reactivation during rapid eye movement sleep promotes its generalization and integration in cortical stores**. *Sleep* 2014, **37**:1061-1075 1075A-1075B.

92. Friedrich M *et al.*: **Generalization of word meanings during infant sleep**. *Nat Commun* 2015, **6**:6004.

93. Hennies N *et al.*: **Sleep spindle density predicts the effect of prior knowledge on memory consolidation**. *J Neurosci* 2016, **36**:3799-3810.

94. Tse D *et al.*: **Schemas and memory consolidation**. *Science* 2007, **316**:76-82.

95. Tse D *et al.*: **Schema-dependent gene activation and memory encoding in neocortex**. *Science* 2011, **333**:891-895.

96. Chadwick MJ *et al.*: **Semantic representations in the temporal pole predict false memories**. *Proc Natl Acad Sci U S A* 2016, **113**:10180-10185.

97. van Kesteren MT *et al.*: **How schema and novelty augment memory formation**. *Trends Neurosci* 2012, **35**:211-219.

98. Ghosh VE *et al.*: **Schema representation in patients with ventromedial PFC lesions**. *J Neurosci* 2014, **34**:12057-12070.

99. Warren DE *et al.*: **False recall is reduced by damage to the ventromedial prefrontal cortex: implications for understanding the neural correlates of schematic memory**. *J Neurosci* 2014, **34**:7677-7682.

100. 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.

101. Coutanche MN, Thompson-Schill SL: **Fast mapping rapidly integrates information into existing memory networks**. *J Exp Psychol Gen* 2014, **143**:2296-2303.

102. Bauer PJ *et al.*: **Productive extension of semantic memory in school-aged children: relations with reading comprehension and deployment of cognitive resources**. *Dev Psychol* 2016, **52**:1024-1037.

103. Jimura K *et al.*: **Relatedness-dependent rapid development of brain activity in anterior temporal cortex during pair-association retrieval**. *Neurosci Lett* 2016, **627**:24-29.

104. Kumaran D, Ludwig H: **Transitivity performance, relational hierarchy knowledge and awareness: results of an instructional framing manipulation**. *Hippocampus* 2013, **23**:1259-1268.

105. Greene AJ *et al.*: **An FMRI analysis of the human hippocampus: inference, context, and task awareness**. *J Cogn Neurosci* 2006, **18**:1156-1173.

106. Henke K, Reber TP, Duss SB: **Integrating events across levels of consciousness**. *Front Behav Neurosci* 2013, **7**:68.

107. Munnelly A, Dymond S: **Relational memory generalization and integration in a transitive inference task with and without instructed awareness**. *Neurobiol Learn Mem* 2014, **109**:169-177.

108. Wimmer GE, Shohamy D: **Preference by association: how memory mechanisms in the hippocampus bias decisions**. *Science* 2012, **338**:270-273.