Opinion
A Closer Look at the Hippocampus and Memory

Joel L. Voss,[1,*] Donna J. Bridge,[1] Neal J. Cohen,[2] and John A. Walker[1]

Current interpretations of hippocampal memory function are blind to the fact that viewing behaviors are pervasive and complicate the relationships among perception, behavior, memory, and brain activity. For example, hippocampal activity and associative memory demands increase with stimulus complexity. Stimulus complexity also strongly modulates viewing. Associative processing and viewing thus are often confounded, rendering interpretation of hippocampal activity ambiguous. Similar considerations challenge many accounts of hippocampal function. To explain relationships between memory and viewing, we propose that the hippocampus supports the online memory demands necessary to guide visual exploration. The hippocampus thus orchestrates memory-guided exploration that unfolds over time to build coherent memories. This new perspective on hippocampal function harmonizes with the fact that memory formation and exploratory viewing are tightly intertwined.

A New View of Memory Formation

Episodes of experience unfold over time and comprise various inter-related stimuli. **Episodic memory** (see Glossary) requires binding together these stimuli and their spatial, temporal, and conceptual relationships to form coherent memory representations [1,2]. Because perception has limited bandwidth, only a fraction of all the information comprising an episode will be effectively 'sampled' by an individual. It is therefore straightforward to assume that the resulting episodic memories will selectively include this sampled information. The majority of our perceptual experience is visual, and memory experiments typically use visual stimuli. **Visual exploration** is therefore necessary to sample stimuli in these experiments. Visual exploration is a pervasive behavior that fundamentally determines the information available for memory formation, but it has mysteriously gone unmeasured in the vast majority of experiments on memory.

In this Opinion we argue that existing data are generally not sufficient for distinguishing brain activity related to memory (and hypothesized memory-related variables) from activity related to viewing behavior. We go on to propose that viewing behavior is not merely a confound to be eliminated from memory studies, but that visual exploration is itself a memory-formation process that is essentially linked to hippocampal function. In the framework we propose, memory formation is not a static event, but rather an active process that is shaped by the way in which memory is used to guide ongoing exploration. In this active-memory framework, the hippocampus is a crucial participant in the bidirectional interaction of memory and exploration processes that are iteratively engaged over the course of learning so as to build episodic memories. Many fMRI experiments on episodic memory formation therefore may have actually identified neural correlates of memory-guided exploration. We offer several suggestions on how future research could focus more acutely on the memory–exploration dynamics that we believe are a fundamental part of memory formation and hippocampal function.

Trends

Memory experiments do not typically measure exploratory viewing behavior, and therefore the observed neural signals can reflect an unknown mixture of processing related to memory, perception, and visual exploration.

Experiments that quantify viewing behaviors during memory formation suggest that important memory–viewing interactions have been missed in previous research, warranting re-evaluation of conclusions about memory mechanisms supported by structures such as the hippocampus.

The hippocampus contributes to viewing during memory formation by providing online memory representations to guide effective exploration, which results in coherently organized memories.

This new theoretical perspective suggests that the hippocampus and viewing are tightly intertwined because hippocampal contributions to memory formation unfold over the timecourse of an episode in synchrony with the timecourse of viewing behavior.

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[2]Department of Psychology, University of Illinois Urbana-Champaign, Urbana, IL, USA

*Correspondence:
joel-voss@northwestern.edu
(J.L. Voss).

fMRI Confounds Hiding in Plain View

Visual exploration has astonishing speed and complexity, with an average of approximately four to five visual fixations to distinct and idiosyncratically selected portions of the environment made every second [3], including during memory experiments (Figure 1A). The stimulus durations typical of memory experiments (approximately 0.5–6 s) therefore permit substantial visual exploration. These characteristics of viewing behavior provide stiff challenges to experiments on memory.

Memory experiments without knowledge of moment-to-moment viewing behavior are therefore problematic because viewing determines the content available for memory [4], including complex content such as the temporal order in which information is viewed [5]. Thus, even though the same stimuli can be presented repeatedly in a memory task (i.e., during study and again at test), the idiosyncratic nature of visual exploration results in, effectively, different information being viewed, in different orders, and with different timings across subjects and repetitions (Figure 1A). This is problematic for interpretations of results from these experiments in several ways. For instance, many theoretical accounts of memory stress the importance of

(A) Idiosyncratic viewing location, order, and timing

Fixation onsets and durations

Sub1
Sub2
Sub3

0 1 2 3 4 5 6 7 8 9 10
Viewing time (s)

Fixation locations

0–3 s
3–6 s
6–10 s

(B) Correlation of complexity, viewing, and activity

Viewing fixation = ○

Dog

fMRI activity

Stimulus visual complexity

(C) Exploration correlated with memory formation

Simple stimuli – weaker correlation | Complex stimuli – stronger correlation

Shrub → Later forgotten
○ → *Later remembered*
Rhode → *Later remembered*
Harp → Later forgotten

→ Later forgotten
→ *Later remembered*
→ *Later remembered*
→ Later forgotten

Trends in Cognitive Sciences

Figure 1. The Complexity of Visual Exploration Is a Challenge for Memory Experiments. (A) Viewing data from three representative subjects are shown for one scene stimulus from a memory experiment using typical study conditions [71]. Visual fixations are plotted as colored circles, with the radius indicating fixation duration and the center indicating fixation onset. The locations of these fixations within the scene are shown in several-second intervals. Viewing behavior was highly idiosyncratic in time and space, including for the first 3-s interval (the approximate duration of stimuli in many memory experiments). For the entire group (3-s n = 21), the average overlap between any two subjects in viewing the same locations of any scene (36 scenes total) was only 56%. (B) Hippocampal subsequent memory effects measured with fMRI are more robust for stimuli of higher complexity [9]. The richness of viewing behavior also increases with stimulus complexity, as shown here by purple circles to indicate typical viewing fixations. (C) As reviewed in the text, stimuli with greater amounts of visual exploration are likely to be better remembered, and this is especially true for stimuli of relatively higher complexity. Hippocampal subsequent-memory effects (later-remembered versus later-forgotten stimuli), which are only robust for complex stimuli, therefore could reflect activity related to visual exploration.
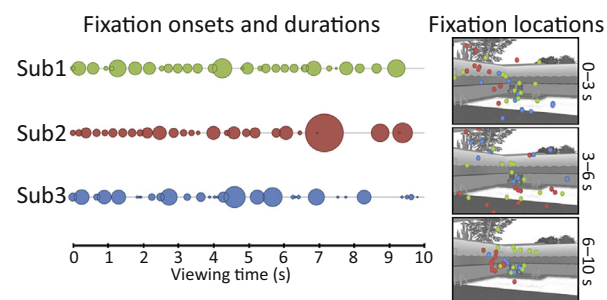
Glossary

Episodic memory: memory for episodes of experience, including the storage and recall of sights, sounds, location, time, and other contextual information that define an event. The defining quality of episodic memory for the present purposes is that it requires binding together of these arbitrarily inter-related episodic fragments into an integrated relational memory representation.

Online memory representation: the ongoing maintenance of memory in an active state. Typically observed by measuring behaviors that reflect memory, but that are expressed continuously via behavior when all relevant stimuli are simultaneously available (i.e., no interposed study–test delay) or over extremely brief interposed retention intervals (i.e., hundreds of milliseconds), rather than via delayed memory testing.
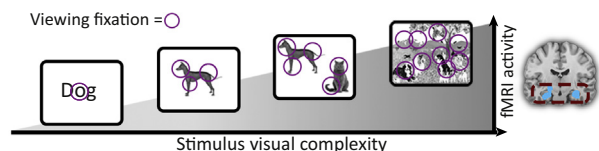
Subsequent memory effects: patterns of neural activity reflecting operations that predict successful memory performance in a delayed test. Test performance is used to back-sort study trials, for instance categorizing those stimuli that are later correctly remembered versus those that are later forgotten. Comparisons between categories such as later-remembered and later-forgotten yield subsequent memory effects.

Visual exploration: the process by which a complex visual stimulus is sampled piecemeal via distinct visual fixations. This usually involves saccadic eye movements that direct visual fixations to important aspects of the environment.
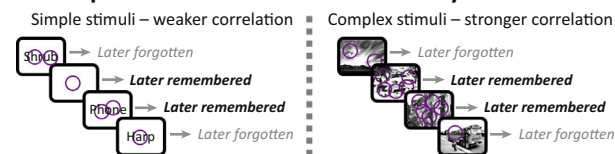
Box 1. Viewing, Study–Test Perceptual Overlap, and Memory

Theories of transfer-appropriate processing suggest that experience of the same information at study and at test is crucial for memory [66–68]. Because nameable stimuli are rapidly identified within approximately one fixation, study–test conceptual overlap will frequently occur, whereas perceptual overlap will vary depending on viewing behavior over the course of the study and test trials (Figure I). Memory can be supported by both conceptual and perceptual overlap, with differential emphasis being based on the type of stimulus and test format [69]. For instance, in one study [70] priming, which is generally thought to reflect implicit memory, was enhanced by maintaining central fixation during study, presumably because this maximized study–test perceptual overlap. By contrast, explicit recognition memory benefited from more-widespread sampling at study, likely because this helped to create conceptually differentiated memories that could later be recalled. Patterns of viewing thus influence study–test perceptual and conceptual overlap, and could therefore be partly responsible for cognitive and neural distinctions between implicit and explicit memory in experiments that do not monitor or control viewing. Interestingly, fMRI activity of the hippocampus has been associated with viewing the same portions of similarly configured scenes at study and at test, suggesting that hippocampal activity is sensitive to study–test perceptual overlap [71]. Study–test overlap in viewing behavior is therefore a crucial but mostly unexplored variable in memory experiments.
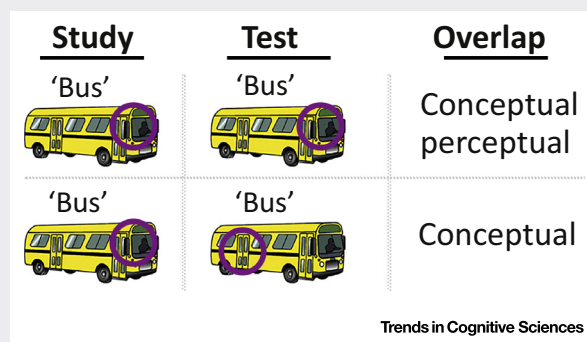

Figure I. Influence of Viewing on Perceptual and Conceptual Overlap between Study and Test. Purple circles indicate hypothetical viewing locations at study and at test, demonstrating how the same stimulus can foster both conceptual and perceptual study–test overlap depending on viewing at both occasions.

overlap between stimuli at study and test, and the perceptual overlap between study and test is unknown unless viewing behavior is measured (Box 1).

Viewing behavior varies in complexity across different categories of stimuli and across different experimental contexts. This variation also poses many interpretive challenges. For example, the earliest neuroimaging studies on memory formation used visually simple stimuli (words or simple nameable objects) and did not identify hippocampal activity [6,7]. When fMRI experiments started to employ material of greater complexity, hippocampal activity correlates were identified more consistently [8], prompting researchers to conclude that "activation of the hippocampal formation . . . is dependent upon the type and complexity of the information presented in the stimuli being encoded" [8]. Although methodology also varied among these early studies, the relationship between hippocampal activity and stimulus complexity has been confirmed by quantitative meta-analysis. That is, fMRI **subsequent memory effects** in the hippocampus are greater when complex graphical information is used as the memoranda (pairs of objects and scenes) compared to more simplistic graphical information (single objects), which yields greater subsequent memory effects than words [9]. This pattern of hippocampal activity is widely believed to reflect the greater associative memory demands required of stimuli of higher complexity. However, complex visual stimuli also require greater amounts of exploratory viewing (Figure 1B). fMRI activity in these studies therefore cannot be attributed to memory rather than exploratory viewing because these variables are highly correlated across levels of stimulus complexity.

Exploratory viewing is a strong predictor of successful memory formation, and especially for complex stimuli. For example, memory performance is improved when subjects freely view face

stimuli compared to when they maintain central fixation, demonstrating the memory-enhancing effect of exploratory viewing [10]. Furthermore, heightened visual exploration enhances memory encoding of scenes and complex material [11–14]. Complex visual stimuli afford the possibility of substantial exploration differences between the later-remembered and later-forgotten conditions, but these differences could even occur for relatively simple stimuli such as words, which are visually explored [15]. Therefore, fMRI subsequent memory effects defined by comparisons of subsequently remembered versus forgotten items could in many cases also serve as comparisons of higher versus lower exploratory viewing (Figure 1C). This is especially true for stimuli of higher complexity, which are also the stimuli that support robust hippocampal subsequent memory effects. The interpretation that follows from this reasoning is that the fMRI correlates of memory formation identified in experiments with relatively complex visual stimuli (i.e., the majority of all such studies conducted for the past 20 years) reflect some unknown amount of memory, exploratory viewing, or their interaction.

Essentially the same reasoning applies to many fMRI studies that attempt to characterize how memory is affected by various cognitive variables such as attention, emotion, intentionality, and

---

Box 2. Viewing-Related Complications

Cognitive constructs that influence memory and hippocampal function often also robustly influence viewing behavior. It is therefore ambiguous whether their influences on memory should be considered as direct effects of the cognitive variables of interest versus indirect effects of those cognitive variables on viewing behavior. Some examples are given below.

Intentional Remembering and Forgetting. Intentional remembering increases memory and hippocampal activity and, unsurprisingly, increases viewing behavior [72]. Influences of intentional remembering on memory therefore cannot be easily separated from the effects of intentionality on viewing behavior. Intentional forgetting decreases memory and reduces hippocampal activity [73]. It is unknown whether intentional forgetting changes viewing behavior because this possibility has not been systematically tested.

Emotion. Emotional stimulus content influences memory and hippocampal activity, including enhancements in the case of emotional content and reductions for accompanying neutral content [74]. Viewing is unsurprisingly biased towards emotional content. Some evidence suggests that the effects of emotion on memory are slightly more than would be expected due solely to preferential viewing of emotional stimuli [75,76]. However, viewing behavior is rarely considered in studies on emotion–memory interactions.

Attention. Attention in memory studies is usually defined as a state-related variable via requirements that subjects attend to specific qualities of stimuli, with corresponding effects on memory and hippocampal activity [77,78]. Viewing behavior is dynamic (see Figure 1A in main text) and has little resemblance to state-like attention conditions. Attention prioritization can also be distinct from viewing behavior (i.e., covert attention). Although attention shares functional neuroanatomy with oculomotor control [79], the extent to which attention effects on memory and hippocampal activity are due to viewing behavior is unclear.

Curiosity. Curiosity about stimuli such as written trivia questions enhances memory and alters hippocampal activity and interaction with reward-related regions [80]. Curiosity also changes viewing behavior during reading [81]. Effects of subjective states such as curiosity on memory and hippocampal activity could therefore result from viewing behavior, which is strongly influenced by a variety of subjective states [82,83].

Reward/Value. Stimulus reward value and expectation of such reward have been reported to influence memory, hippocampal activity, and hippocampal interaction with reward-related regions [84,85]. Value and expectation strongly influence viewing [86,87], which has not been considered in most studies on reward and its expectation.

Scene and/or Spatial Cognition. Many studies highlight scene memory processing [88] or spatial processing as unique functions supported by the hippocampus. Stimulus type (scenes and spatial environments versus non-scenes and non-spatial stimuli) is almost perfectly confounded with both viewing behavior and relational memory demands [36,89]. The ability for spatial/scene theoretical views to account for visual exploration (or for relational memory demands) is very limited.

Aging. Many studies have investigated age-related differences in memory and its hippocampal fMRI correlates. Age-related differences in viewing patterns are robust and predict memory performance [12,72]. The extent to which these viewing changes contribute to memory and hippocampal activity in older adults is unknown.

---

many others (Box 2). This is because the experimental conditions used to manipulate these cognitive variables can strongly influence viewing behavior, and therefore the cognitive variables of interest are often confounded with viewing behavior. Although it is tempting to interpret the effects of various cognitive manipulations on memory as reflecting how 'states of mind' can influence memory, it would be equally fitting to consider many of these cognitive variables as creating 'states of viewing behavior' that influence memory. New research that accounts for viewing will be necessary to determine whether the cognitive variables *per se*, as opposed to their unintended effects on viewing behavior, constitute the key factor influencing hippocampal activity and memory in these studies.

Although we have focused on memory formation, the same logic applies to memory retrieval. Viewing behavior differs for categories of retrieval such as novelty, familiarity, and recollection [16–19]. Viewing behavior can signal memory processing even during free-recall tasks where no stimuli are present to view [20], and can reflect complex qualities of memory such as temporal order [21] and competition between memories [22,23]. Viewing thus complicates the interpretation of neural correlates of retrieval.

It is also important to note that interpretive complications are not limited to fMRI. For instance, although electroocular nuisance signals can be removed from magnetoencephalography (MEG)/electroencephalography (EEG) data to obtain 'clean' neural recordings, the influences of viewing behavior on neural activity remain, and thus experiments using these methods have the same interpretive limitations as fMRI ([24] for a brief discussion). Likewise, analyses using pattern-classification methods (e.g., multivariate pattern analysis or representational similarity analysis) could exacerbate the interpretive uncertainties introduced by viewing behavior. Evidence for specific fMRI patterns thought to reflect 'memory representations' could instead reflect subtle differences in the classification of stimuli that are viewed differently across experimental conditions [25]. The idiosyncratic nature of viewing behavior (Figure 1A) exacerbates this situation because it nullifies standard counterbalancing of stimuli to experimental conditions, and weak counterbalancing can yield classification results that reflect these nuisance variables rather than conditions of interest [26]. Further, as described below, individuals with hippocampal lesions demonstrate abnormal viewing behaviors, and the extent to which their memory impairments are secondary to viewing abnormality requires careful analysis of viewing behavior. Thus, regardless of the methods used to investigate the brain, it is crucial that viewing behavior is considered.

Simply measuring viewing behavior is not by itself sufficient for unambiguously distinguishing activity related to memory versus viewing behavior. For example, a recent study found that hippocampal activity increased for scenes containing geometrically impossible configurations of objects relative to scenes with geometrically possible configurations, leading to the conclusion that the hippocampus is crucial for binding together novel object configurations [27]. Eye-movement tracking showed that subjects made more fixations within the region of the scene containing the impossible objects. Viewing behavior thus differed fundamentally for the possible versus impossible scenes. Therefore, even though viewing behavior was measured, its differences among the key conditions of interest render interpretation of the hippocampal fMRI signals ambiguous. Measurement of viewing behavior is essential to draw appropriate conclusions regarding the nature of the observed fMRI activity, even if it does not allow one to differentiate viewing behavior from the crucial variable of interest.

We propose that, instead of simply measuring viewing, researchers should incorporate eye-movement measures into the study design to test the independence and interactivity of viewing behavior versus the other memory constructs of interest. In the next sections we describe findings from such research. Although the extent to which previous findings need

reconsideration remains to be seen, the main point that we wish to make is that efforts to account for viewing behavior will yield richer understanding of the cognitive and neural mechanisms for memory than can be achieved when viewing behavior is ignored.

Evidence Linking the Hippocampus to Viewing Behavior

Neural recordings obtained directly from the hippocampus via depth electrodes in nonhuman primates and in humans have indicated that viewing behavior is strongly related to hippocampal activity (reviewed in [28]). For instance, visual fixations are associated with evoked activity of hippocampus and surrounding medial temporal cortical areas [29]. Hippocampal theta-band oscillatory activity has been strongly implicated in memory [30]. Visual fixations are generated at theta frequency [3], and correspond to resetting of the phase of hippocampal theta oscillations [31,32]. Crucially, the reliability of theta phase-reset by visual fixations correlated with successful memory formation [31]. Furthermore, other neural signals of memory processing by hippocampus include sharp-wave ripples [33], which have been observed during visual exploration in the nonhuman primate [34], particularly for fixations in close proximity to target stimuli in a memory task [35]. In studies with rodents, memory is usually expressed via exploration, making it difficult to determine the extent to which hippocampal activity in these studies reflects memory processing versus exploration, including sensory sampling and exploration-related aspects of spatial navigation [36]. However, exploration and memory can be segregated more readily via eye-movement tracking in primates, providing evidence that hippocampal activity reflects spatial and non-spatial memory that is strongly influenced by visual exploration [37].

Human hippocampal activity measured with fMRI has been found to correlate across memory-formation trials with the number of visual fixations made per trial [38]. Furthermore, this relationship between hippocampal activity and viewing was present for novel faces, but not for repeated faces, suggesting that hippocampal activity reflected the role of viewing behavior in memory formation. Notably, had viewing not been measured in this study, a simple repetition effect (i.e., old vs new activity difference) would have been identified, thereby distorting conclusions regarding the nature of the observed hippocampal activity. In a similar experiment, healthy control subjects generated higher fixation counts for stimuli that were later remembered versus later forgotten, but a patient with hippocampal damage failed to show this relationship [39], indicating that the hippocampus is necessarily involved in the increased viewing behavior normally associated with memory formation. Collectively, these studies suggest that viewing behavior is an integral part of the memory formation process supported by the hippocampus.

Hippocampal Contributions to Exploratory Viewing for Memory Formation

The aforementioned findings establish an association between hippocampal activity and viewing behavior during memory formation, but what is the nature of this association? In particular, does the hippocampus have any direct role in driving viewing behavior, or is its association with viewing merely a byproduct of its role in memory? If the role of the hippocampus in viewing behavior were only secondary, then its activity in relation to viewing would simply reflect the bottom-up flow of visual information locked to the onset of fixations. That is, each fixation could provide a 'bolus' of visual input to the dorsal and ventral visual streams that converge on the hippocampus, and in this sense hippocampal activity associated with viewing could merely reflect this fixation-locked visual input. By contrast, we propose an active-memory role for the hippocampus, whereby it provides memory signals that direct the exploratory viewing process that occurs during learning (Figure 2, Key Figure). We thus suggest that memory formation is an active and ongoing process shaped by exploration that is strategically implemented based on hippocampus-dependent memory signals.

Key Figure

Two Possibilities for the Role of the Hippocampus in Viewing Behavior
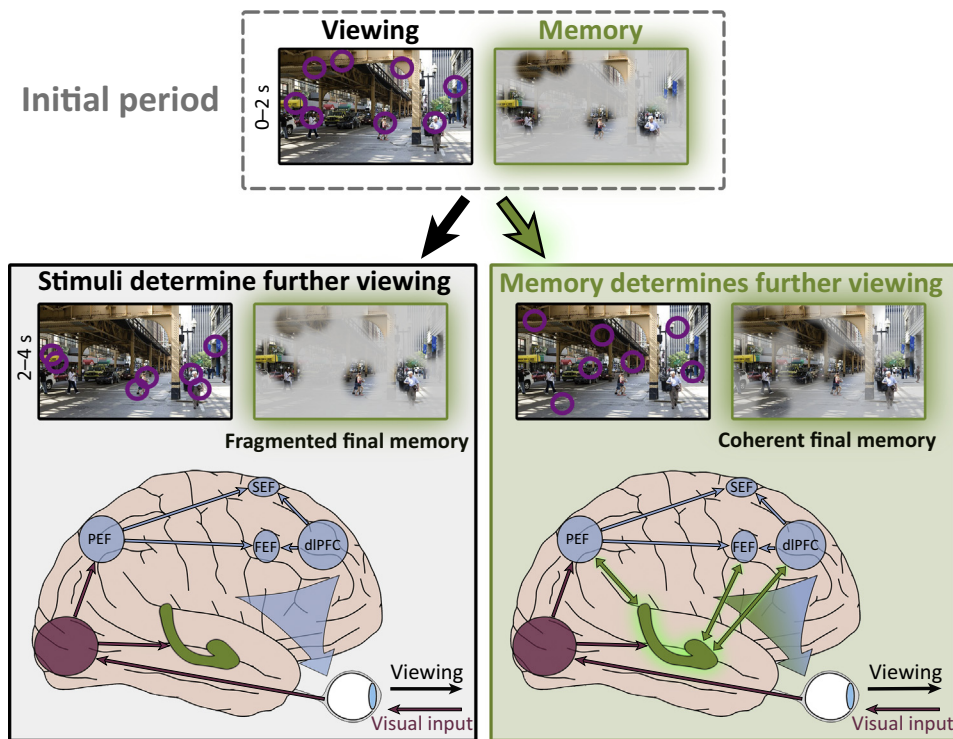
Trends in Cognitive Sciences

Figure 2. When studying a complex visual stimulus such as a scene, the viewing history at any given moment will constrain the memory representation that is formed (top). Factors other than memory, such as the perceptual salience of stimuli, can determine further viewing (left-bottom panel). In this scenario, the current status of memory is ignored when determining what to explore next. Thus, the final memory representation that results is likely to be fragmented and incomplete. Visual information would be independently sent to hippocampus for memory processing and to oculomotor control regions for determination of further viewing. By contrast, our active-memory hypothesis is that the status of memory at any moment is used to direct further viewing (right-bottom panel). Crucial information such as weak memory for a subset of items or their inter-relationships could therefore be used to direct exploration to the information that is needed to build a coherent memory representation. In this scenario, the hippocampus would interact with cortical oculomotor control regions such that online memory representations could be used to drive exploration. Note that for simplicity of illustration we define an 'initial period' that is distinct from 'further viewing', although we propose that memory–exploration interplay is a dynamic process occurring in a continuous fashion as each new visual fixation is made. Cortical oculomotor control regions are taken from [90]: parietal eye field (PEF), frontal eye field (FEF), supplementary eye field (SEF), and dorsolateral prefrontal cortex (dlPFC). Purple indicates visual input and cortical visual processing regions. Subcortical projections of cortical oculomotor regions are not shown for simplicity, and are illustrated via an arrow projecting to the eye. Anatomical substrates for functional interactions of hippocampus with these cortical oculomotor control regions include dense structural interconnections of hippocampus with FEF, SEF, and dlPFC [91].

Indeed, exploratory viewing enhances subsequent memory [10,40–43], and hippocampal damage impairs viewing during memory formation [39]. This suggests that exploratory viewing is an integral part of the hippocampus-dependent memory formation process, rather than a mere byproduct. Our position is that the hippocampus is responsible for providing access to very short-term relational memory signals that are needed for effective visual exploration. There are several mechanisms by which these signals could benefit memory formation. For example, building an episodic memory requires binding together various features that are individually

experienced across space and time. Therefore, an ongoing memory for these features and their relationships would allow additional viewing of stimuli/relationships with relatively weak memory representations, thereby benefiting memory for the entire episode (Figure 2).

Substantial evidence suggests that hippocampus is a likely source of the brief-interval memory signals that are needed to guide ongoing visual exploration. For instance, individuals with amnesia due to bilateral lesions of the hippocampus demonstrate marked deficits in memory tasks involving brief retention intervals (i.e., seconds), in addition to their long-term memory impairments. These deficits occur particularly for novel visual stimuli that necessitate binding of multiple arbitrarily related stimulus features, such as novel shapes and novel associations among collections of objects and spatial locations [44–48], and therefore reflect failures of relational memory processing that occur with little or no interposed study–test delay. Hippocampal neuronal activity likewise carries evidence for memory maintenance across brief retention intervals [49,50]. This evidence is consistent with the notion that hippocampus supports **online memory representation**, and particularly of the relations among the features of complex stimuli and/or episodes [51]. By providing an ongoing memory for the relationships among the stimuli comprising an episode, the hippocampus could thereby yield the signals needed to guide exploration in a manner that fosters a comprehensive memory of all relevant relationships (e.g., revisiting weakly linked stimuli to allow further encoding of their relationships). Thus, the contribution of hippocampal online memory representation to exploration could be particularly suited to the construction of episodic memories with high cohesiveness among constituent parts (Figure 2).

Direct evidence for the role of these online memory functions of hippocampus in guiding visual exploration comes from studies that tested the interaction between exploration and memory. For example, in an experiment on object–location associative memory, superior memory formation resulted from self-directed visual exploration, compared to viewing the same information in a passive condition that lacked self-directed exploration [42]. The beneficial effects of self-directed exploration on memory formation have been associated with increased hippocampal fMRI connectivity with other memory-related regions [42], as well as with increased hippocampal theta activity measured with MEG during spatial navigation [52]. Furthermore, lesions of the human hippocampus impair visual exploration [53], and eliminate the beneficial effects of exploration and of increased viewing on later memory seen in healthy individuals [39,42].

The role of hippocampus in memory-directed visual exploration is further supported by findings of hippocampal contributions to specific memory-related viewing behaviors that are generated during visual exploration. For instance, subjects studying collections of objects generate iterative viewing patterns involving repeat sampling of adjacent objects. These iterative viewing patterns improve memory for those objects viewed iteratively (as opposed to other objects in the same visual displays), and are associated with hippocampal fMRI activity [54]. Iterative viewing patterns are also disrupted in individuals with bilateral hippocampal lesions [54]. In a study using concurrent eye-movement tracking and fMRI, trial-to-trial fluctuations in iterative viewing of novel visual stimuli during a discrimination task correlated with hippocampal fMRI activity [55]. Interestingly, iterative viewing could serve to increase processing and binding of interrelationships among stimuli. Rodents exhibit similar iterative viewing behaviors, which are strongly linked to memory formation [41], are disrupted by hippocampal lesions [56,57], and are associated with hippocampal theta activity and sharp-wave ripples [58,59]. Other self-generated exploratory behaviors that enhance learning in the rodent (i.e., rearing) have been independently associated with increased hippocampal activity [60]. These findings are all consistent with our proposal that hippocampal online memory representations are used to

guide exploration to form more-cohesive episodic memories than would result without such hippocampal involvement (Figure 2).

We [51] and others [58] have proposed that the hippocampus provides online memory representations to be used by other regions, such as those involved in oculomotor control, to guide visual exploration (Figure 2). These memory–exploration interactions are likely to be bidirectional, and normally occur in rapid iteration during memory formation, making them extremely difficult to isolate using methods with low temporal resolution such as fMRI. Nonetheless, we recently segregated brief-delay memory retrieval from ensuing exploration using an artificially imposed delay period [61]. In doing so, we were able to distinguish hippocampal activity associated with short-delay memory retrieval from frontoparietal activity associated with specific memory-related viewing patterns during subsequent exploration. Although relatively artificial circumstances were needed to separate memory from exploratory viewing (because these normally occur rapidly and iteratively), the role of hippocampus in online memory representation during visual exploration has been supported for variety of scenarios, including relatively naturalistic memory-guided exploration tasks [42,51,54,58,62].

Concluding Remarks

We first considered several possible ramifications of viewing behavior in memory experiments that do not either control or measure it, despite using stimuli that promote complex viewing patterns. Viewing determines the nature of visual input, and therefore has substantial face-validity as a key factor in almost any experimental design. Given that 'nothing in neurobiology makes sense except in the light of behavior' [63], it is imperative that rigorous measures of behavior, including viewing, are employed. By ignoring viewing behavior, experimenters tacitly assume that the memory effects of conditions of interest are unrelated to the viewing behaviors that are often drastically affected by these conditions. We have considered only a subset of the challenges that viewing behavior poses for the interpretation of memory experiments (Boxes 1 and 2).

How should we make progress in understanding neural mechanisms for memory given pervasive viewing behaviors? As suggested above, simply using eye-movement tracking in common memory paradigms will not 'solve' the issues that we raise. This is because viewing behavior is often highly correlated with the conditions of interest, and thus cannot be easily removed from the experiment (e.g., [27]) (Box 2). Carefully designed experiments that either control/limit viewing behavior or include conditions that segregate memory processing from viewing behavior are needed. Notably, elimination of viewing behavior via brief stimulus presentations [as are typical in some EEG/event-related potential (ERP) research] effectively removes any possible 'confound', but results are effectively blind to the memory–exploration dynamic that is likely to be fundamental to normal memory and hippocampal function.

Although necessary, specifying the relationships among memory formation, exploratory viewing, and the hippocampus will be challenging (see Outstanding Questions). The fact that viewing behavior is so highly correlated with key variables that affect memory suggests that viewing is highly relevant to memory function across a wide spectrum of circumstances (Box 2). Furthermore, exploration extends beyond vision. It is a fundamental property of all perceptual systems and potentially even occurs in cognitive spaces [64]. For instance, nasal breathing is a marker of exploration that both entrains hippocampal theta activity and is associated with episodic memory formation [65]. Across all modalities, experiments that address the memory–exploration interface would benefit from neural recording methods that, unlike fMRI, match the temporal resolution of the exploration process, such as electrocorticography.

Outstanding Questions

Can the exploration–memory interface be studied effectively using neural measures with low temporal resolution (e.g., fMRI, brain lesions)? Do the artificial circumstances needed to disaggregate memory from exploration in such circumstances fundamentally alter the relationship between viewing and memory?

If existing fMRI memory studies were to be updated with eye-movement tracking, how many conclusions regarding hippocampal involvement in memory would remain unchanged?

Do 'standard' neural signals of memory formation and retrieval persist in the absence of exploration? Are there distinct hippocampal signals of memory formation and retrieval during exploration versus memory formation that is independent from exploration?

Given that exploration can be driven by both perceptual and memory-related factors, how can the balance between perceptual versus mnemonic influences on exploration best be experimentally controlled? For instance, does this balance vary reliably over time, such as with greater initial perceptual influences and increased memory influences as the memory representation evolves?

How specifically can viewing patterns indicative of memory-guided exploration be linked to hippocampal activity via invasive neural recordings? Are hippocampal memory signals always time-locked to eye movements, or can memory representations evolve and change in relation to viewing behavior but without strict temporal synchronization to visual fixations?

Although we have discussed viewing behavior as a 'confound' that could potentially complicate the interpretation of a variety of neuroimaging studies, it is important to emphasize our view that hippocampus-dependent memory is an essential contributor to visual exploration, and that further investigation of the memory–viewing interface is imperative. The same logic applies to other behaviors that occur during experiments, such as manual responses, which must be considered when interpreting brain activity but that also provide important information on cognitive processing (e.g., reaction-time analysis). Viewing behavior is arguably one of the most important behaviors to study, given that it fundamentally determines the information available for memory, and occurs during visual exploration, which is a crucial aspect of memory formation. Exploratory viewing is thus not a confound to be eliminated, but is a crucial target for study if we are to develop a complete account of the cognitive and neural mechanisms for memory formation.

References

1. Eichenbaum, H. and Cohen, N.J. (2004) *From Conditioning to Conscious Recollection: Memory Systems of the Brain,* Oxford University Press
2. Underwood, B.J. (1969) Attributes of memory. *Psychol. Rev.* 76, 559–573
3. Otero-Millan, J. *et al.* (2008) Saccades and microsaccades during visual fixation, exploration, and search: foundations for a common saccadic generator. *J. Vis.* 8, 21
4. Hollingworth, A. and Henderson, J.M. (2002) Accurate visual memory for previously attended objects in natural scenes. *J. Exp. Psychol.-Human Percept. Perform.* 28, 113–136
5. Zelinsky, G.J. and Loschky, L.C. (2005) Eye movements serialize memory for objects in scenes. *Percept. Psychophys.* 67, 676–690
6. Shallice, T. *et al.* (1994) Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature* 368, 633–635
7. Grasby, P.M. *et al.* (1993) Functional mapping of brain areas implicated in auditory–verbal memory function. *Brain* 116, 1–20
8. Stern, C.E. *et al.* (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. U. S. A.* 93, 8660–8865
9. Kim, H. (2011) Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuroimage* 54, 2446–2461
10. Henderson, J.M. *et al.* (2005) Eye movements are functional during face learning. *Mem. Cognit.* 33, 98–106
11. Loftus, G.R. (1972) Eye fixations and recognition memory for pictures. *Cognit. Psychol.* 3, 525–551
12. Chan, J.P. *et al.* (2011) Can changes in eye movement scanning alter the age-related deficit in recognition memory? *Front. Psychol.* 2, 92
13. Molitor, R.J. *et al.* (2014) Memory-related eye movements challenge behavioral measures of pattern completion and pattern separation. *Hippocampus* 24, 666–672
14. Kafkas, A. and Montaldi, D. (2011) Recognition memory strength is predicted by pupillary responses at encoding while fixation patterns distinguish recollection from familiarity. *Q. J. Exp. Psychol.* 64, 1971–1989
15. Sereno, S.C. and Rayner, K. (2003) Measuring word recognition in reading: eye movements and event-related potentials. *Trends Cogn. Sci.* 7, 489–493
16. Manns, J.R. *et al.* (2000) The visual paired-comparison task as a measure of declarative memory. *Proc. Natl. Acad. Sci. U. S. A.* 97, 12375–12379

17. Althoff, R.R. and Cohen, N.J. (1999) Eye-movement-based memory effect: a reprocessing effect in face perception. *J. Exp. Psychol. Learn. Mem. Cogn.* 25, 997–1010
18. Ryan, J.D. *et al.* (2000) Amnesia is a deficit in relational memory. *Psychol. Sci.* 11, 454–461
19. Kafkas, A. and Montaldi, D. (2012) Familiarity and recollection produce distinct eye movement, pupil and medial temporal lobe responses when memory strength is matched. *Neuropsychologia* 50, 3080–3093
20. Bone, M.B. *et al.* (2017) Eye-movement reinstatement and neural reactivation: testing the Hebbian theory of mental imagery. *bioRxiv* Published online February 17, 2017. http://dx.doi.org/10.1101/107953
21. Pathman, T. and Ghetti, S. (2015) Eye movements provide an index of veridical memory for temporal order. *PLoS One* 10, e0125648
22. Bridge, D.J. and Voss, J.L. (2014) Hippocampal binding of novel information with dominant memory traces can support both memory stability and change. *J. Neurosci.* 34, 2203–2213
23. Williams, C.C. *et al.* (2009) Age differences in what is viewed and remembered in complex conjunction search. *Q. J. Exp. Psychol.* 62, 946–966
24. Griffiths, B. *et al.* (2016) Brain oscillations track the formation of episodic memories in the real world. *Neuroimage* 143, 256–266
25. Huffman, D.J. and Stark, C.E.L. (2017) The influence of low-level stimulus features on the representation of contexts, items, and their mnemonic associations. *Neuroimage* Published online April 8, 2017. http://dx.doi.org/10.1016/j.neuroimage.2017.04.019
26. Todd, M.T. *et al.* (2013) Confounds in multivariate pattern analysis: theory and rule representation case study. *Neuroimage* 77, 157–165
27. Douglas, D. *et al.* (2017) Perception of impossible scenes reveals differential hippocampal and parahippocampal place area contributions to spatial coherence. *Hippocampus* 27, 61–76
28. Meister, M.L. and Buffalo, E.A. (2016) Getting directions from the hippocampus: The neural connection between looking and memory. *Neurobiol. Learn. Mem.* 134, 135–144
29. Ringo, J.L. *et al.* (1994) Eye movements modulate activity in hippocampal, parahippocampal, and inferotemporal neurons. *J. Neurophysiol.* 71, 1285–1288
30. Jutras, M.J. and Buffalo, E.A. (2014) Oscillatory correlates of memory in non-human primates. *Neuroimage* 85, 694–701
31. Jutras, M.J. *et al.* (2013) Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. *Proc. Natl. Acad. Sci. U. S. A.* 110, 13144–13149

32. Hoffman, K.L. *et al.* (2013) Saccades during visual exploration align hippocampal 3–8 Hz rhythms in human and non-human primates. *Front. Syst. Neurosci.* 7, 43

33. Yu, J.Y. and Frank, L.M. (2015) Hippocampal–cortical interaction in decision making. *Neurobiol. Learn. Mem.* 117, 34–41

34. Leonard, T.K. *et al.* (2015) Sharp wave ripples during Visual exploration in the primate hippocampus. *J. Neurosci.* 35, 14771–14782

35. Leonard, T.K. and Hoffman, K.L. (2017) Sharp-wave ripples in primates are enhanced near remembered visual objects. *Curr. Biol.* 27, 257–262

36. Eichenbaum, H. (2017) The role of the hippocampus in navigation is memory. *J. Neurophysiol.* 117, 1785–1796

37. Wirth, S. *et al.* (2017) Gaze-informed, task-situated representation of space in primate hippocampus during virtual navigation. *PLoS Biol.* 15, e2001045

38. Liu, Z.X. *et al.* (2017) Visual sampling predicts hippocampal activity. *J. Neurosci.* 37, 599–609

39. Olsen, R.K. *et al.* (2016) The relationship between eye movements and subsequent recognition: evidence from individual differences and amnesia. *Cortex* 85, 182–193

40. Ploran, E.J. *et al.* (2014) Self-motivated visual scanning predicts flexible navigation in a virtual environment. *Front. Hum. Neurosci.* 7, 892

41. Tolman, E.C. (1938) The determinants of behavior at a choice point. *Psychol. Rev.* 45, 1–41

42. Voss, J.L. *et al.* (2011) Hippocampal brain-network coordination during volitional exploratory behavior enhances learning. *Nat. Neurosci.* 14, 115–120

43. Bridge, D.J. and Voss, J.L. (2015) Binding among select episodic elements is altered via active short-term retrieval. *Learn. Mem.* 22, 360–363

44. Watson, P.D. *et al.* (2013) Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. *Hippocampus* 23, 570–580

45. Warren, D.E. *et al.* (2012) Hiding in plain view: lesions of the medial temporal lobe impair online representation. *Hippocampus* 22, 1577–1588

46. Warren, D.E. *et al.* (2011) Observing degradation of visual representations over short intervals when medial temporal lobe is damaged. *J. Cogn. Neurosci.* 23, 3862–3873

47. Warren, D.E. *et al.* (2010) Medial temporal lobe damage impairs representation of simple stimuli. *Front. Hum. Neurosci.* 4, 35

48. Koen, J.D. *et al.* (2017) Visual short-term memory for high resolution associations is impaired in patients with medial temporal lobe damage. *Hippocampus* 27, 184–193

49. Kaminski, J. *et al.* (2017) Persistently active neurons in human medial frontal and medial temporal lobe support working memory. *Nat. Neurosci.* 20, 590–601

50. Libby, L.A. *et al.* (2014) Medial temporal lobe coding of item and spatial information during relational binding in working memory. *J. Neurosci.* 34, 14233–14242

51. Wang, J.X. *et al.* (2015) Covert rapid action-memory simulation (CRAMS): a hypothesis of hippocampal–prefrontal interactions for adaptive behavior. *Neurobiol. Learn. Mem.* 117, 22–33

52. Kaplan, R. *et al.* (2012) Movement-related theta rhythm in humans: coordinating self-directed hippocampal learning. *PLoS Biol.* 10, e1001267

53. Yee, L.T. *et al.* (2014) The hippocampus uses information just encountered to guide efficient ongoing behavior. *Hippocampus* 24, 154–164

54. Voss, J.L. *et al.* (2011) Spontaneous revisitation during visual exploration as a link among strategic behavior, learning, and the hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 108, E402–E409

55. Voss, J.L. and Cohen, N.J. (2017) Hippocampal–cortical contributions to strategic exploration during perceptual discrimination. *Hippocampus* 27, 642–652

56. Hu, D. and Amsel, A. (1995) A simple test of the vicarious trial-and-error hypothesis of hippocampal function. *Proc. Natl. Acad. Sci. U. S. A.* 92, 5506–5509

57. Bett, D. *et al.* (2012) The neural substrates of deliberative decision making: contrasting effects of hippocampus lesions on performance and vicarious trial-and-error behavior in a spatial memory task and a visual discrimination task. *Front. Behav. Neurosci.* 6, 70

58. Redish, A.D. (2016) Vicarious trial and error. *Nat. Rev. Neurosci.* 17, 147–159

59. Papale, A.E. *et al.* (2016) Interplay between Hippocampal sharp-wave-ripple events and vicarious trial and error behaviors in decision making. *Neuron* 92, 975–982

60. Mun, H.S. *et al.* (2015) Self-directed exploration provides a Ncs1-dependent learning bonus. *Sci. Rep.* 5, 17697

61. Bridge, D.J. *et al.* (2017) Distinct hippocampal versus frontoparietal network contributions to retrieval and memory-guided exploration. *J. Cogn. Neurosci.* Published online May 4, 2017. http://dx.doi.org/10.1162/jocn_a_01143

62. Wang, J.X. and Voss, J.L. (2014) Brain networks for exploration decisions utilizing distinct modeled information types during contextual learning. *Neuron* 82, 1171–1182

63. Shepherd, G. (1988) *Neurobiology.* (2nd edn), Oxford University Press

64. Hills, T.T. *et al.* (2008) Search in external and internal spaces: evidence for generalized cognitive search processes. *Psychol. Sci.* 19, 802–808

65. Zelano, C. *et al.* (2016) Nasal respiration entrains human limbic oscillations and modulates cognitive function. *J. Neurosci.* 36, 12448–12467

66. Noton, D. and Stark, L. (1971) Scanpaths in saccadic eye movements while viewing and recognizing patterns. *Vision Res.* 11, 929–942

67. Morris, C.D. *et al.* (1977) Levels of processing versus transfer appropriate processing. *J. Verbal Learn. Verbal Behav.* 16, 519–533

68. Noton, D. and Stark, L. (1971) Scanpaths in eye movements during pattern perception. *Science* 171, 308–311

69. Voss, J.L. *et al.* (2012) More than a feeling: pervasive influences of memory without awareness of retrieval. *Cogn. Neurosci.* 3, 193–207

70. Willems, S. *et al.* (2010) The mere exposure effect and recognition depend on the way you look! *Exp. Psychol.* 57, 185–192

71. Ryals, A.J. *et al.* (2015) Hippocampal contribution to implicit configuration memory expressed via eye movements during scene exploration. *Hippocampus* 25, 1028–1041

72. Shih, S.I. *et al.* (2012) Aging, eye movements, and object-location memory. *PLoS One* 7, e33485

73. Hulbert, J.C. *et al.* (2016) Inducing amnesia through systemic suppression. *Nat. Commun.* 7, 11003

74. Kensinger, E.A. *et al.* (2007) Effects of emotion on memory specificity: memory trade-offs elicited by negative visually arousing stimuli. *J. Memory Lang.* 56, 575–591

75. Steinmetz, K.R. and Kensinger, E.A. (2013) The emotion-induced memory trade-off: more than an effect of overt attention? *Mem. Cognit.* 41, 69–81

76. Riggs, L. *et al.* (2011) The role of overt attention in emotion-modulated memory. *Emotion* 11, 776–785

77. Aly, M. and Turk-Browne, N.B. (2016) Attention promotes episodic encoding by stabilizing hippocampal representations. *Proc. Natl. Acad. Sci. U. S. A.* 113, E420–E429

78. Chun, M.M. and Turk-Browne, N.B. (2007) Interactions between attention and memory. *Curr. Opin. Neurobiol.* 17, 177–184

79. Corbetta, M. *et al.* (1998) A common network of functional areas for attention and eye movements. *Neuron* 21, 761–773

80. Gruber, M.J. *et al.* (2014) States of curiosity modulate hippocampus-dependent learning via the dopaminergic circuit. *Neuron* 84, 486–496

81. Baranes, A. *et al.* (2015) Eye movements reveal epistemic curiosity in human observers. *Vision Res.* 117, 81–90

82. Castelhano, M.S. *et al.* (2009) Viewing task influences eye movement control during active scene perception. *J. Vis.* 9, 6

83. Yarbus, A.L. (1967) *Eye Movements and Vision,* Plenum Press

84. Murty, V.P. *et al.* (2016) Distinct medial temporal networks encode surprise during motivation by reward versus punishment. *Neurobiol. Learn. Mem.* 134, 55–64

85. Adcock, R.A. *et al.* (2006) Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron* 50, 507–517

86. Gottlieb, J. *et al.* (2014) Attention, reward, and information seeking. *J. Neurosci.* 34, 15497–15504

87. Kafkas, A. and Montaldi, D. (2015) Striatal and midbrain connectivity with the hippocampus selectively boosts memory for contextual novelty. *Hippocampus* 25, 1262–1273

88. Zeidman, P. *et al.* (2015) Constructing, perceiving, and maintaining scenes: hippocampal activity and connectivity. *Cereb. Cortex* 25, 3836–3855

89. Cohen, N.J. and Eichenbaum, H. (1991) The theory that wouldn't die: a critical look at the spatial mapping theory of hippocampal function. *Hippocampus* 1, 265–268

90. Pierrot-Deseilligny, C. *et al.* (2004) Eye movement control by the cerebral cortex. *Curr. Opin. Neurol.* 17, 17–25

91. Shen, K. *et al.* (2016) An anatomical interface between memory and oculomotor systems. *J. Cogn. Neurosci.* 28, 1772–1783