



Review

Getting directions from the hippocampus: The neural connection between looking and memory



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ABSTRACT

Investigations into the neural basis of memory in human and non-human primates have focused on the hippocampus and associated medial temporal lobe (MTL) structures. However, how memory signals from the hippocampus affect motor actions is unknown. We propose that approaching this question through eye movement, especially by assessing the changes in looking behavior that occur with experience, is a promising method for exposing neural computations within the hippocampus. Here, we review how looking behavior is guided by memory in several ways, some of which have been shown to depend on the hippocampus, and how hippocampal neural signals are modulated by eye movements. Taken together, these findings highlight the need for future research on how MTL structures interact with the oculomotor system. Probing how the hippocampus reflects and impacts motor output during looking behavior renders a practical path to advance our understanding of the hippocampal memory system.

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1. Introduction

For decades, looking behavior has been used to assess memory (Hannula et al., 2010), and recent efforts have identified subtle changes in viewing behavior that indicate memory. However, we currently know very little about the relationship between medial temporal lobe (MTL) structures that are necessary for memory and the oculomotor system that controls eye movements. In an attempt to motivate future research that investigates the neural mechanisms by which memory interacts with eye movement, here we review studies demonstrating the influence of memory on looking behavior, describe related neural signals in MTL structures, and discuss potential points of interaction between the MTL and oculomotor systems.

The study of biological systems in more natural settings, where experimental stimuli are less artificial and required behavior is less controlled, has been growing. This approach has been explicitly called for in certain fields, such as vision, for the purpose of better exposing nervous system operations (Churchland, Ramachandran,

& Sejnowski, 1994; Findlay & Gilchrist, 2003; Geisler & Ringach, 2009). Because vision naturally relies heavily upon eye movement, the case was made to study vision in the context of looking behavior instead of using the more common technique of requiring subjects to fixate for long periods of time while visual stimuli are presented peripherally (Findlay & Gilchrist, 2003). A similar argument for greater laboratory focus on natural behavior has also been made for the study of eye movements themselves (Tatler, Hayhoe, Land, & Ballard, 2011), where this approach has yielded impressive insight into what constitutes normal behavior. We wish to extend this idea by advocating for a more natural approach to the study of memory. As we describe below, behavioral paradigms that allow both humans and non-human primates to freely view images have uncovered a range of effects that experience has on eye movement. Importantly, these modifications in viewing behavior with experience have often been shown to depend upon the integrity of MTL structures, and eye movements have been shown to modulate MTL neural activity. We will review these findings and explore how future research of hippocampal function can benefit through discovery of how the MTL reflects and affects eye movement.

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2. Why study the neurophysiology of memory through eye movement?

2.1. Primacy of looking for primates

Vision is a primate's primary sensory modality. Unlike rodents, for example, who boast an impressive olfactory ability, we boast an impressive visual ability, and chiefly use vision to extract information from the world around us. It is interesting to note that in the English language, we use terms associated with vision as a synonym for "understand": "I see your point", "show me what you mean", "we don't have the same views", "her innovative vision for the future", "it opened my eyes." Primates' natural inclination toward visual sensing can also be illustrated by the fact that monkeys do not have to be trained to look at pictures, and readily initiate image viewing even without reward offered by the experimenter (Wilson & Goldman-Rakic, 1994). Monkeys show a preference for a picture over a blank screen (Humphrey, 1972) and look longer at pictures than a homogenous color field (Wilson & Goldman-Rakic, 1994). Additionally, memory for what we view is impressive, and a large literature demonstrates that humans can achieve almost perfect recognition of previously viewed images despite testing sets of hundreds to thousands of images (Shepard, 1967; Standing, 1973; Standing, Conezio, & Haber, 1970).

The mechanics of looking heavily influence our memory because the visual input that feeds memory is highly discretized by eye movements. Specifically, primate looking behavior is constituted by fixations and saccades that break up visual information. "Saccades" are rapid, ballistic eye movements that direct the central, high-resolution areas of our retinæ around the environment. By contrast, "fixations" are the still periods of time between eye movements, the retinal image is relatively stable and detailed information can be extracted from visual stimuli. Despite the uniform perception we have of looking at a stable visual scene, we are in fact making saccades about three to five times each second, and we actually only see visual detail within about two degrees of visual angle (about the width of your thumbs held next to each other at arm's length) of the world at any one moment (Findlay & Gilchrist, 2003). Recognition memory for objects more than two degrees away from fixation is impoverished, suggesting that direct fixation is necessary for an object within a visual scene to be reliably encoded during natural viewing (Nelson & Loftus, 1980). Fixation count is arguably a currency of memory, as the strength of picture recognition depends more on the number of fixations made during encoding (Kafkas & Montaldi, 2011; Molitor, Ko, Hussey, & Ally, 2014) than how long the picture was viewed (Loftus, 1972). As spatially specific indicators of attention and perception, fixations determine what we remember within pictures, and congruently, stronger memory is associated with image regions that contained more fixations during encoding (Irwin & Zelinsky, 2002; Pertzov, Avidan, & Zohary, 2009; van der Linde, Rajashekar, Bovik, & Cormack, 2009).

2.2. Looking behavior guided by memory

Measuring the novelty preference in looking behavior is one way memory can be assessed in the laboratory in a relatively natural context (Buffalo et al., 1999; Manns, Stark, & Squire, 2000; Zola et al., 2000). Most often used by developmental psychologists to observe memory in human infants (Reynolds, 2015), preferential looking at novel objects is a memory metric that capitalizes on primates' innate preference for novelty and their ability to form a robust memory for an image viewed only a few seconds.

The simplest method for quantifying novelty preference in looking behavior is to compare the overall time spent looking at novel

and repeated stimuli. In the "Visual Paired Comparison Task," novelty preference is quantified as the proportion of time spent looking at a novel image when it is presented alongside a previously viewed image. Using this measure, healthy human adults, infants, and monkeys exhibit a preference for looking at novel stimuli (Buffalo et al., 1999; Crutcher et al., 2009; Fagan, 1970; Manns et al., 2000; McKee & Squire, 1993; Nemanic, Alvarado, & Bachevalier, 2004; Zola, Manzanares, Clopton, Lah, & Levey, 2012; Zola et al., 2000). In the "Visual Preferential Looking Task" (Fig. 1A), developed for performing neurophysiology experiments of novelty preference in monkeys (Wilson & Goldman-Rakic, 1994), only one image is presented at a time, and if the monkey looks away, the image vanishes and the trial ends. Comparing overall looking time for novel and repeated images also reveals novelty preference in this task (Jutras, Fries, & Buffalo, 2009; Killian, Jutras, & Buffalo, 2012; Wilson & Goldman-Rakic, 1994).

Another measure of viewing behavior that reflects stimulus novelty is the number of fixations made while freely viewing visual scenes. Several studies have reported that more fixations are made within novel scenes, compared with repeated or familiar scenes (Althoff & Cohen, 1999; Hannula et al., 2010; Ryan, Althoff, Whitlow, & Cohen, 2000; Smith, Hopkins, & Squire, 2006; Smith & Squire, 2008). This effect was also observed within a virtual 3D environment (Kit et al., 2014) in which, in a more real-life scenario, subjects became familiar with the environment by performing virtual household tasks over several days of sessions. Novel features introduced into the virtual environment were fixated upon with increased probability relative to control objects.

Both the timing and distribution of eye movements have also been shown to indicate whether a stimulus is encoded in memory. A general effect has been observed that people make fixations of shorter duration when they view novel, compared to repeated images (Smith et al., 2006). The duration of fixations has also been linked to the strength of memory encoding, as fixations are shorter when subjects view novel images that are later reported as recollected compared to those that are subsequently forgotten (Kafkas & Montaldi, 2011). People also sample (fixate) fewer image regions when viewing a repeated image (Althoff & Cohen, 1999; Smith & Squire, 2008; Smith et al., 2006), and this change in behavior has been linked to awareness that an image is repeated (Smith & Squire, 2008). Fixations have also been reported to be more clustered across the image space when subjects initially view a later-recalled image compared to an image that was subsequently only judged as familiar (Kafkas & Montaldi, 2011).

In another paradigm which exploits novelty preference to measure memory, one portion of the scene is altered between novel and repeat viewing, i.e., an object in the scene is removed, replaced, or moved to a new location in the scene. In this case, subjects spend more time looking at the altered region of the previously seen image. Subjects view the altered region longer, make more fixations within it (Fig. 1B), and make more eye movement transitions into and out of it (Ryan et al., 2000; Smith & Squire, 2008; Smith et al., 2006). Interestingly, this behavior is apparent even when subjects are instructed simply to view the images, and are under no explicit experimental instruction to remember the stimuli or identify changes (Ryan et al., 2000; Smith & Squire, 2008).

Although there is general agreement that hippocampal-dependent memory is typically accompanied by conscious awareness, some disagreement exists about whether awareness is required for memory-guided viewing. For example, human subjects preferentially viewed a manipulated region of an image without correctly reporting awareness of the manipulation on some trials (Ryan et al., 2000). Hannula et al. (2010) posit that these results support the idea that awareness is not necessary for memory-guided viewing behavior. However, later studies did not replicate this result, and found that awareness was required for

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