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## Imbalance of incidental encoding across tasks: An explanation for non-memory-related hippocampal activations?

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### Abstract

Functional neuroimaging studies have increasingly noted hippocampal activation associated with a variety of cognitive functions such as decision-making, attention, perception, incidental learning, prediction and working memory, which have little apparent relation to declarative memory. Such findings might be difficult to reconcile with classical hippocampal lesion studies that show remarkable sparing of cognitive functions outside the realm of declarative memory. Even the oft-reported hippocampal activations during confident episodic retrieval are not entirely congruent with evidence that hippocampal lesions reliably impair encoding but inconsistently affect retrieval. Here we explore the conditions under which the hippocampus responds during episodic recall and recognition. Our findings suggest that anterior hippocampal activity may be related to the imbalance of incidental encoding across tasks and conditions, rather than due to retrieval, per se. Incidental encoding and hippocampal activity may be reduced during conditions where retrieval requires greater attentional engagement. During retrieval, anterior hippocampal activity decreases with increasing search duration and retrieval effort, and this deactivation corresponds with a coincident impaired encoding of the external environment (Israel, Seibert, Black, & Brewer, 2010; Reas & Brewer, 2013; Reas, Gimbel, Hales, & Brewer, 2011). In light of this emerging evidence, we discuss the proposal that some hippocampal activity observed during memory retrieval, or other non-memory conditions, may in fact be attributable to concomitant encoding activity which is regulated by the attentional demands of the principal task.

### Keywords

memory; hippocampus; encoding; retrieval; fMRI

### Introduction

Lesion, electrophysiology and neuroimaging studies on humans, monkeys and rodents have established that the hippocampus is critical for declarative memory (for review see Eichenbaum, 2004; Squire, Stark, & Clark, 2004). Neuroimaging studies report activation of the human hippocampus during a range of experimental paradigms evoking the formation or retrieval of episodic memories (Cohen, et al., 1999; Schacter & Wagner, 1999). The hippocampus is frequently activated during successful memory encoding (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner, et al., 1998), recognition of previously encountered stimuli (Gabrieli, Brewer, Desmond, & Glover, 1997; Stark & Squire, 2000), retrieval of stronger memories (Wais, 2011; Wais, Squire, & Wixted, 2010) or recollection of contextual details (Daselaar, Fleck, & Cabeza, 2006; Eldridge, Knowlton, Furmanski,

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Bookheimer, & Engel, 2000; Yu, Johnson, & Rugg, 2011). Such activations are often identified by contrasting signal levels between conditions using cognitive subtraction techniques intended to isolate the targeted memory function, but which may incidentally capture additional mnemonic and non-mnemonic processes. Thus, it is challenging to disentangle activity related to retrieval from that driven by interwoven encoding or non-mnemonic processes using neuroimaging techniques alone, which cannot inform whether these neural operations are essential for memory recovery.

Neuropsychological studies of patients with selective lesions can provide more definitive insight into the necessity of the hippocampus for specific cognitive functions. The earliest evidence that the hippocampus is critical for learning declarative information came from patient H.M. Following bilateral medial temporal lobe resection, including the hippocampus, he exhibited selective deficits in establishing new memories, yet had relatively spared retrograde memory abilities (Scoville & Milner, 1957), indicating that the medial temporal lobe is essential to acquire new episodic memories, but not to retrieve previously stored and consolidated memories. Some studies of patients with more isolated hippocampal damage demonstrate impaired recollection, yet intact familiarity-based memory, while others report deficits in both recognition processes (Jenison, Kirwan, Hopkins, Wixted, & Squire, 2010; Yonelinas, et al., 2002). However, since both the study and retrieval phases of these investigations occurred post-lesion, they do not distinguish between deficits at the time of memory acquisition or retrieval. Studies that allow for such disambiguation by testing the integrity of autobiographical memories acquired before amnesia onset report mixed findings. Some patients with hippocampal lesions manifest anterograde and temporally graded retrograde amnesia, with memory deficits for events following and immediately preceding amnesia onset (Manns, Hopkins, & Squire, 2003). Yet others report amnesia extending back throughout the lifespan, albeit again in a time-dependent manner (Bartsch, Dohring, Rohr, Jansen, & Deuschl, 2011), or that the degree of retrograde amnesia depends on the extent of hippocampal damage (Rosenbaum, et al., 2008). In rodents with hippocampal lesions, the timespan of retrograde amnesia differs between spatial and fear memories (Winocur, Sekeres, Binns, & Moscovitch, 2013), suggesting that the nature of the memory is an additional factor determining how long a declarative memory remains hippocampus-dependent. Retrieval can also be supported by the parahippocampal gyrus recently after memory acquisition, and by surrounding neocortex following reorganization over time (Squire & Wixted, 2011), accounting for some observations of hippocampus-independent retrieval. Critically, these lesion studies, which serve as a gold standard for whether a brain region makes a necessary contribution to a given function, consistently report intact non-declarative memory performance. Those impairments that are not strictly mnemonic, such as future simulation and imagining, appear closely related to memory-based processes (Addis & Schacter, 2012).

Together, these lesion studies indicate that the hippocampus is not required for non-mnemonic functions, but is essential for forming episodic memories. Yet, neuroimaging studies imply a rather promiscuous hippocampal involvement across a breadth of cognitive domains, including reward, emotion, working memory and decision-making (Curtis, Zald, Lee, & Pardo, 2000; Elliott, Friston, & Dolan, 2000; Koelsch, Fritz, DY, Muller, & Friederici, 2006; Viard, Doeller, Hartley, Bird, & Burgess, 2011). Reports of such non-memory, and some retrieval-related, activations are thus incongruent with more decisive evidence from amnesic patients indicating a selective role for the hippocampus in establishing declarative memories. How then, does one reconcile the frequent, yet variable, conditions under which hippocampal responses are observed during neuroimaging studies? This review will discuss several lines of evidence from functional magnetic resonance imaging (fMRI) studies that may account for discrepant reports of some hippocampal activations, which may be misattributed to processes that are independent of the

hippocampus or preserved following hippocampal lesions. These findings suggest that hippocampal responses during recognition or recall are less directly linked to retrieval than to the modulation of encoding processes by concomitant non-mnemonic task components.

## Hippocampal deactivation during retrieval

Recent fMRI findings reveal that anterior hippocampal activity is reduced during cued recall relative to both baseline and a non-memory control task (Israel, et al., 2010; Reas, et al., 2011; Figure 1), suggesting either that the hippocampus is not reliably engaged by retrieval or that any retrieval-related response may be overridden by competing influences. Although there are challenges to interpreting the baseline blood-oxygen-level-dependent (BOLD) signal during unrestrained periods which may evoke a range of mental states (Gusnard & Raichle, 2001), the rest and control conditions in these studies are not expected to engage memory to a greater extent than during the recall task. Thus, any retrieval activity would be expected to present as a task-positive response, rather than the observed task-negative deflection from baseline. Follow-up investigations revealed that the magnitude of this reduction corresponds with the difficulty of the retrieval trial (Reas, et al., 2011). Specifically, the anterior hippocampus deactivates during recall of strongly remembered paired associates and deactivates further during the attempted recall of weaker memories (Figure 1B). Such evidence is consistent with numerous reports of higher hippocampal activity for more confident retrieval or successful recollection (Cohen, et al., 1999; Schacter & Wagner, 1999), yet conflicts with the interpretation that such relative differences are driven by recollection-related task-positive activations.

Neuroimaging studies that report retrieval-related activations often compare successful and failed retrieval, recollection and familiarity, or memory strength levels. These subtractions coincidentally contrast levels of other processes highly integrated with retrieval, including cognitive control to execute directed recall efforts, sustained attention to search through a memory store, re-encoding of a recovered memory, or working memory engaged during post-retrieval monitoring. If functionally connected to brain networks subserving such concomitant processes, the hippocampus could correlate with activity that covaries with attention or cognitive control. In turn, these interactions might serve to modulate hippocampus-dependent memory functions such as monitoring and encoding the ongoing stream of experience. This may explain the paradoxical finding of hippocampal activity levels during recollection that lie intermediate between levels during weak retrieval and non-retrieval conditions (Figure 1B).

Although hippocampal activity increases with the strength of the target memory, it also correlates with the response time of the retrieval decision, posing a challenge to disentangling effects of memory strength from associated attentional factors. Israel et al. (2010) and Reas et al. (2011) report that anterior hippocampal activity negatively correlates with response times, such that longer duration retrieval attempts more strongly deactivate the hippocampus. This correlation is present during both cued recall and recognition tasks and persists after controlling for differences in memory strength (Reas & Brewer, 2013; Reas, et al., 2011), but is not observed during a non-memory classification task (Israel, et al., 2010) (Figure 2A, Figure 3A). These findings suggest that the hippocampal response during both recognition and recall is modulated by response time-dependent factors, and that this relationship is stronger under conditions demanding attentional control of mnemonic operations. Since psychological models of memory propose that sequential search processes in retrieval can be estimated with response times (Sternberg, 1966), a correlation between response times and the retrieval-related BOLD response indicates a potential modulatory effect of memory search on the hippocampus. While the attentional demands of the retrieval effort thus appear to strongly regulate the hippocampus, additional research is warranted to

examine the influence of other sub-processes of retrieval, including working memory, error monitoring and post-retrieval evaluation.

These findings do not imply that the hippocampus subserves memory search. Rather, it may receive input from upstream regions directing search operations, which in turn regulate persistent memory functions performed by the hippocampus. Functional connectivity studies have revealed that the hippocampus is not only a component of a cortical memory system, but, likely through indirect connections via the parahippocampal gyrus (Ward, et al., 2013), also correlates with a set of regions referred to as the default network (Greicius, Srivastava, Reiss, & Menon, 2004; Huijbers, Pennartz, Cabeza, & Daselaar, 2011; Vincent, et al., 2006). The default network, comprising regions of medial frontal, medial and lateral parietal, and temporal cortex, is most active during passive rest or internally-directed cognition and is deactivated during goal-directed, externally-orientated tasks (Anticevic, et al., 2012; Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, et al., 2001). The magnitude of this task-induced suppression correlates with greater task difficulty (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), retrieval effort and trial-by-trial recall response times, and is greater for “know” than “remember” recognition judgments (Gimbel & Brewer, 2011; Reas, et al., 2011, Figure 3). Thus, input from the default network may account for some correlations between hippocampal activity and fluctuations in attention or cognitive control. It has been proposed that task-induced deactivations serve to reallocate resources away from inefficient neural processing towards those that support the intended neural operation (Drevets, et al., 1995; McKiernan, et al., 2003). Under this interpretation, cognitive control and attention engaged during goal-oriented retrieval might inhibit hippocampal memory processes, for example, monitoring and encoding the external environment, that interfere with successful recovery of the target memory trace.

### **Hippocampal responses during retrieval track incidental encoding**

We have thus far discussed evidence that hippocampal activity during retrieval can correlate with cognitive functions outside the domain of declarative memory, but have yet to address how these interactions relate to the established function of the hippocampus in forming new episodic memories (Scoville & Milner, 1957; Squire, et al., 2004). It is feasible that fluctuations in hippocampal activity track ongoing encoding processes even during states that do not intentionally manipulate encoding. Features of episodic events are continually monitored and encoded during intentional retrieval, serving to re-encode previously encountered stimuli (Lars Nyberg, Cabeza, & Tulving, 1996) and to form novel memories for both task-relevant (Buckner, Wheeler, & Sheridan, 2001; Stark & Okado, 2003) and task-irrelevant (Huijbers, Pennartz, Cabeza, & Daselaar, 2009) background information. Furthermore, incidental learning during retrieval can be facilitated (Zeithamova, Dominick, & Preston, 2012) or impaired (Huijbers, et al., 2009) by retrieval and correlates with activity in the hippocampus (Stark & Okado, 2003) and other medial temporal lobe regions (Huijbers, et al., 2009). Therefore, hippocampal responses that vary according to retrieval success, strength or effort, may alternatively be attributable to how these conditions regulate encoding of the ongoing stream of experience, rather than or in conjunction with, veritable retrieval processes.

Based upon previously discussed findings that anterior hippocampal activity tracks retrieval effort, a recent study examined how retrieval search influences incidental encoding, and regulates encoding-sensitive hippocampal responses (Reas & Brewer, 2013). In this experiment, subsequent memory was evaluated for pictures presented during recognition of strong and weak verbal memories. Picture encoding was less successful during attempts to retrieve lower strength memories or when the recognition response was prolonged, indicating that higher levels of search impair concurrent encoding processes (Figure 4A).

These findings expand upon prior work that reported diminished subsequent memory for scenes presented during successful recognition and suggested that retrieval and encoding competitively regulate medial temporal lobe activity (Huijbers, et al., 2009). Together, these studies demonstrate that multiple aspects of a retrieval task, including successful recovery, search or memory strength can collectively regulate hippocampal functions associated with simultaneous memory formation.

Replicating numerous prior studies, Reas and Brewer (2013) found that hippocampal responses were greater during successful than failed recognition and during retrieval of stronger memories. But critically, bilateral anterior hippocampus deactivated and the signal magnitude tracked encoding success, with stronger negative deflections when concurrent encoding failed (Figure 4B). As also observed in cued recall (Reas, et al., 2011), the BOLD response in this region negatively correlated with recognition response times (Figure 3A), suggesting that anterior hippocampal activity is reduced both when search duration is increased and incidental encoding is unsuccessful. Thus, while hippocampal activity often correlates with retrieval success or strength, it is also modulated by the degree to which coincident encoding functions are suppressed during effortful, goal-directed retrieval attempts.

### Functional specialization of anterior and posterior hippocampus

The previously discussed findings demonstrate that hippocampus-mediated encoding operations that are persistently online may act concurrently, and possibly interactively, with retrieval. If the hippocampus is necessary both for acquiring and retrieving memories, dynamic shifts between these functions might either competitively engage a region, or concurrently recruit distinct specialized regions. Both encoding-sensitive deactivations and retrieval-sensitive activations are present during a given retrieval task (Reas & Brewer, 2013; Figure 4B), as are task-positive activations to “remember” recognition judgments and task-negative activations to “know” judgments (Gimbel & Brewer, 2011) (Figure 2B). However, these retrieval-related hippocampal responses were non-uniform, exhibiting a transitioning response gradient along the longitudinal axis of the hippocampus (Figure 5). Whereas the anterior hippocampus is consistently deactivated while tracking retrieval effort, search and incidental encoding, posterior regions exhibit positively activating responses to retrieval success (Figures 1B, 4B). Yet, even posterior activity that covaries with retrieval success or confidence may be influenced by the simultaneous re-encoding of a recovered memory, as similar BOLD patterns are engaged at retrieval as during encoding (Kuhl, Rissman, Chun, & Wagner, 2010; L. Nyberg, Habib, McIntosh, & Tulving, 2000; Woodruff, Johnson, Uncapher, & Rugg, 2005).

Although additional research is needed to thoroughly disentangle effects of these concomitant memory processes within the hippocampus, evidence of regional specialization for memory functions in the hippocampus may account for its heterogeneous responses. In the human and animal hippocampus, highly specialized behavioral functions, anatomical circuitry and gene expression patterns distinguish subregions (dentate gyrus, CA3, CA1, subiculum) as well as anterior versus posterior regions. For instance, computations such as pattern separation or completion that possibly subserve the creation, evaluation or recovery of memories are preferentially performed by distinct subregions (Bakker, Kirwan, Miller, & Stark, 2008; Chen, Olsen, Preston, Glover, & Wagner, 2011; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2011). Functional dissociations within subfields have been observed in rodents, with ventral and dorsal dentate gyrus respectively associated with anxiety and contextual learning (Kheirbek, et al., 2013). Human neuroimaging studies provide further evidence for the involvement of anterior regions in encoding, novelty, relational binding and

the construction of future events, and posterior regions in retrieval, recollection or elaboration of past and future events (Addis & Schacter, 2008; Daselaar, et al., 2006; Giovanello, Schnyer, & Verfaellie, 2004; Lepage, Habib, & Tulving, 1998; Poppenk, McIntosh, Craik, & Moscovitch, 2010; Prince, Daselaar, & Cabeza, 2005), consistent with distinct anterior versus posterior anatomical circuitry (Aggleton, 2011). Collectively, these findings suggest that the hippocampus supports both encoding and retrieval, but that these functions may be non-uniformly distributed. The interdependent, reciprocally regulating nature of these processes complicates efforts to cleanly dissociate their influences on hippocampal activity, and, further, suggests additional caution in interpreting modulations of hippocampal activity during non-mnemonic tasks.

## Future Directions

Together, the discussed findings help reconcile inconsistent reports of hippocampal involvement in non-mnemonic processes. Given evidence that retrieval search regulates hippocampus-mediated encoding, it is feasible that other non-mnemonic processes similarly modulate ongoing memory functions. For example, additional research will help determine how working memory, error monitoring or post-retrieval evaluation during retrieval influence encoding of the external environment or the retrieved memory. Future fMRI studies will benefit from assessing the directionality of parametric influences on these activations with impulse-response curves to supplement simple subtraction techniques, accounting for response times and considering covariance with cortical regions modulated by task difficulty. Functional and anatomical connectivity analyses as well as integrated multimodal neuroimaging techniques will aid in elucidating the neural circuitry underlying hippocampal-cortical interactions along with their spatial distribution and temporal dynamics.

## Conclusion

Despite conclusive evidence that the hippocampus is essential for the construction of new episodic memories, contention remains over its contribution to memory retrieval and non-memory-based functions that inconsistently elicit hippocampal responses. There is emerging evidence that such conditions, which engage a breadth of cognitive processes encompassing cognitive control, sustained attention, working memory and error monitoring, may modulate concurrent, persistent background encoding functions. These findings provide a cohesive interpretation for hippocampal activity that inherently correlates with non-memory components of a diverse set of tasks, but is fundamentally driven by the degree to which the hippocampus is actively monitoring and encoding the external environment.

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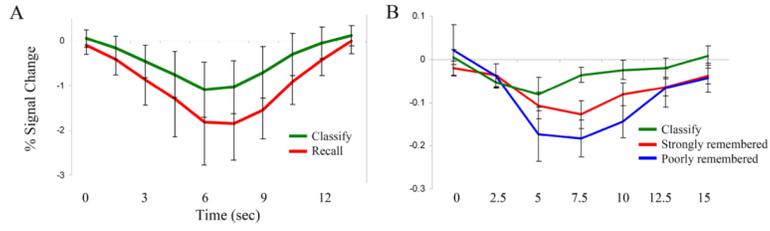
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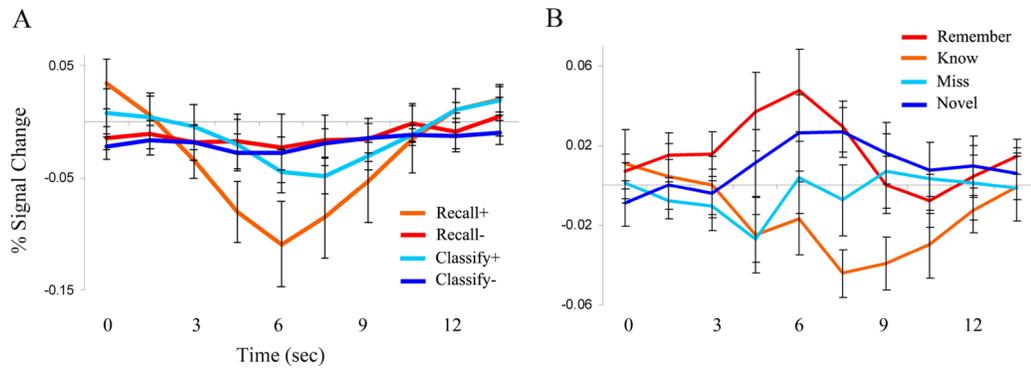
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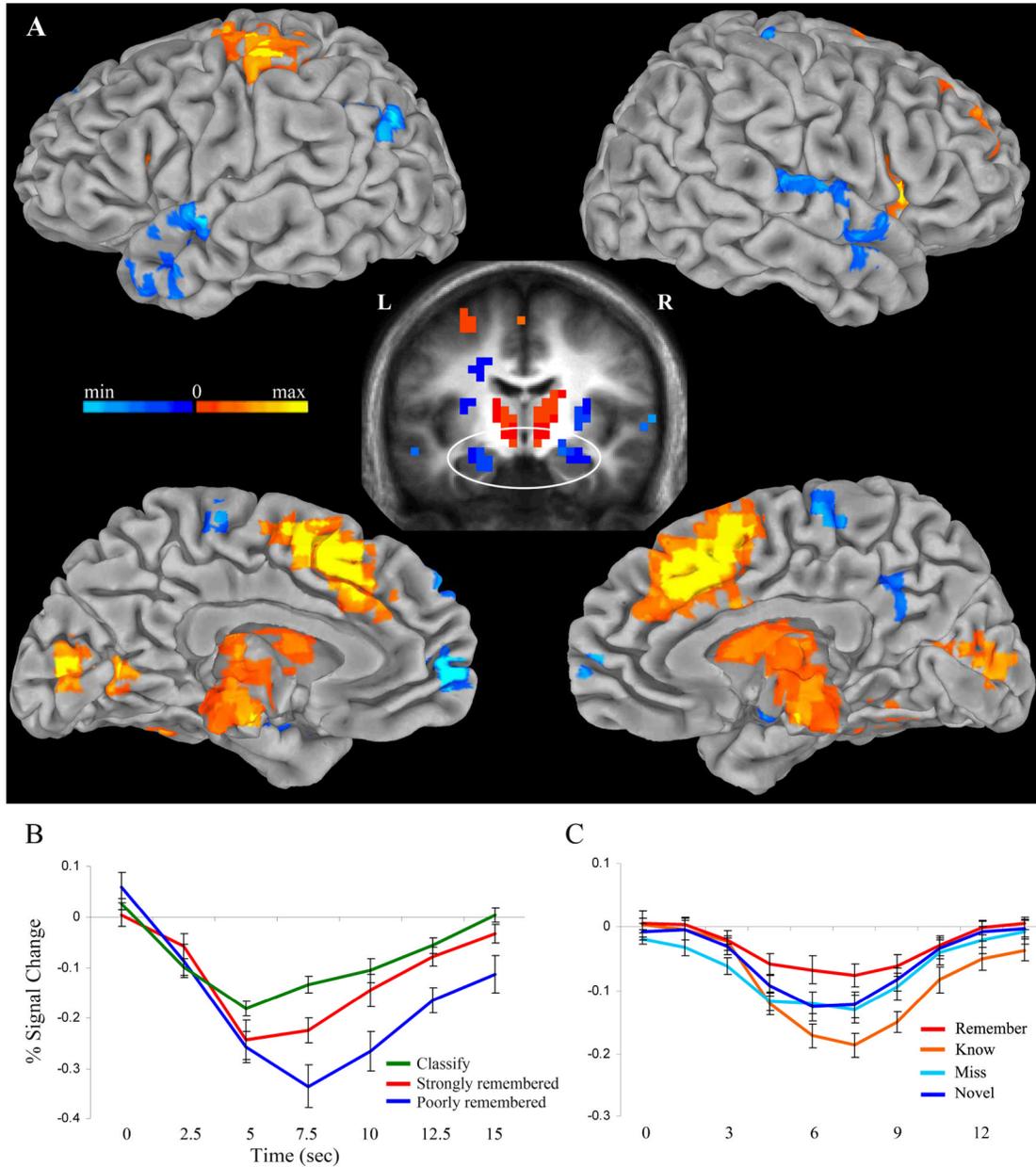
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**Figure 1.** Hippocampal deactivation during cued recall. A. Right anterior hippocampus was more strongly deactivated ( $p < .05$ ) during recall of visual paired associates than during a non-memory classification task. (Israel, et al., 2010). B. Left anterior hippocampus was more deactivated ( $ps < .01$ ) during recall of strongly remembered verbal paired associates than during classification, and during recall of poorly versus strongly remembered associates (Reas, et al., 2011). Error bars represent standard error of the mean.

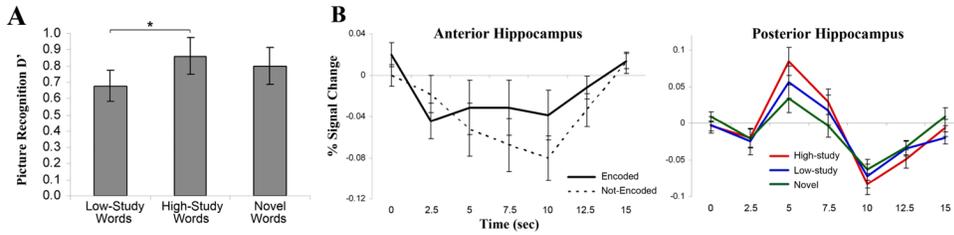


**Figure 2.** Hippocampal modulation by response time, recognition judgment. A. Deactivation of the right anterior hippocampus is greater for recall trials with longer (Recall+) versus shorter (Recall-) response times, but does not differ between long and short classification (Classify+ vs. Classify-) responses (Israel, et al., 2010). B. “Remember” recognition judgments elicit task-positive responses, whereas “know” judgments elicit task-negative responses in bilateral hippocampus (Gimbel & Brewer, 2011). Error bars represent standard error of the mean.

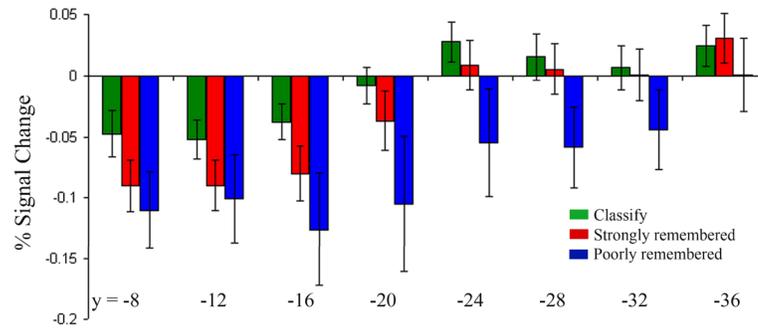


**Figure 3.**

Hippocampus and default network deactivation by response time, search and strength. A. BOLD responses in bilateral anterior hippocampus, medial prefrontal cortex, posterior cingulate, superior temporal and left inferior parietal cortex were negatively correlated with recognition response times ( $p < .01$ , cool colors). (Reas & Brewer, 2013) B, C. Average default network activity is more strongly reduced during recall of poorly than strongly remembered paired associates (B, Reas, et al., 2011) and during “know” than “remember” recognition responses (C, Gimbel & Brewer, 2011) ( $ps < .01$ ). Error bars represent standard error of the mean.



**Figure 4.** A. Recognition  $d'$  scores for pictures presented during a word recognition test. Incidental encoding was impaired for pictures presented concurrently with words studied once compared to words studied four times. \*  $p < .01$ . B. Impulse response curves for the anterior and posterior bilateral hippocampus during a word recognition test with incidental picture encoding. Responses in anterior hippocampus ( $y = -7$  to  $-18$ ) were modulated by picture encoding, whereas activity in posterior hippocampus ( $y = -27$  to  $-38$ ) differed according to word retrieval condition ( $ps < .05$ ). (Reas & Brewer, 2013) Error bars represent standard error of the mean.



**Figure 5.** Hippocampal activity during a non-memory classification task, cued recall of strongly remembered word pair associates and cued recall of poorly remembered word pair associates. Beta-values ( $\pm$  standard error) are presented for 4 mm slices along the longitudinal axis of the bilateral hippocampi, from anterior (left) to posterior (right). (Reas, et al., 2011)