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Editorial

Hippocampal interactions with brain networks that influence learning & memory

The hippocampus and surrounding medial temporal lobe (MTL) cortical structures play a critical role in long-term learning and memory (cf. Squire & Wixted, 2011). However, these structures do not operate in isolation. This special issue combines research studies and empirical reviews that examine the structure and function of larger scale brain networks and patterns of connectivity that contribute to, and influence, the effectiveness of hippocampus-supported memory encoding, storage, and retrieval. Questions about how these brain networks are reorganized or disrupted as a consequence of normal aging or disease states are considered, and models of network interactions with the hippocampus are described. A major goal of this issue was to cast a wide net by examining these larger scale networks in the context of both the human and non-human animal literatures and across a range of methodological approaches (e.g., electrophysiology, resting state connectivity, task-based functional neuroimaging, brain stimulation techniques). Special emphasis was placed on a variety of cognitive processes that impact learning and memory outcomes – e.g., increasing the likelihood that information will be well encoded and subsequently retrieved, or reducing the fidelity or accessibility of previously encoded memory representations. For example, several papers examine changes in connectivity patterns with the hippocampus as a function of the emotional processing requirements of a task. In short, this special issue provides novel insights into the collective contributions of distributed brain networks to learning and memory, which has most often been viewed through a narrow lens focused on the hippocampus (or the MTL) in isolation.

The special issue begins with two papers that examine changes in the anatomical integrity, connectivity profiles, and oscillatory signatures of the hippocampus as a consequence of healthy aging. **Foster, Picklesimer, Mulligan, & Giovanello** examine age-related changes in functional coupling of the hippocampus with the default mode network during relational memory encoding. Results indicated that a hippocampal seed region was functionally coupled with a greater number of default mode network structures in older, as compared to younger, adults – an effect that was evident despite the absence of significant differences in memory performance. The authors speculate about this observation, suggesting that it is unlikely to be a consequence of compensatory mechanisms, and propose instead that there is inefficiency in the transition between network states with advanced age. **Rondina, Olsen, McQuiggan, et al.** used magnetoencephalography to determine whether changes in neural oscillatory signatures of relational memory occur as a consequence of healthy aging. Past work from the same authors with younger adults (Olsen, Rondina, Riggs, Meltzer, & Ryan, 2013) indicated that increased theta power in the hippocampus and medial prefrontal cortex (PFC) predicted successful short-term retention of spatio-temporal relationships among a set of presented objects. In the current study, healthy older adults showed no decrements in performance of this task, and there was no evidence for significant hippocampal atrophy; there were, however, considerable differences in the neural oscillatory networks that were engaged during task performance. Theta power was reduced in the hippocampus relative to younger adults, as were alpha and beta power across much of the cortex. The authors conclude that older adults recruit a wider network of brain structures to achieve the same level of relational memory performance as their younger counterparts and suggest that neural oscillatory measures are especially sensitive to age-related brain changes.

Increasingly, there is interest in how localized brain damage affects network connectivity among parts of the brain that are not directly compromised by injury, surgical procedures, or disease (cf. Finke, Bruehl, Düzel, Heekeren, & Plonder, 2013). The next article in this issue **(Meng, Hu, Bachevalier, & Zhang)** examines changes in the connectivity patterns of dorsolateral PFC in monkeys with neonatal hippocampal lesions. This work is especially important because it indicates that patterns of spared and impaired performance in brain-damaged populations may reflect unanticipated changes in network connectivity rather than the absence of a particular brain structure. Results from their study, which examined resting state functional connectivity using a DLPFC seed region, indicated that interconnectivity between this region and a core set of structures that constitute the working memory network was reduced following neonatal hippocampal lesions. Moreover, reduced connectivity between DLPFC and visual cortical areas was correlated with deficits in the performance of working memory tasks. This work has critical implications for neuropsychological investigations in humans and lesion studies in laboratory animals. As the authors indicate, it will be important to determine whether there is similar evidence for working memory network disruption associated with adult-onset hippocampal lesions.

The next several papers in this special issue address questions about the impact of emotional context or processing on connectivity patterns and hippocampus-supported learning and memory. In the behavioral literature there are marked effects of threat and reward on successful learning and memory. The studies reported here provide new insights into networks of brain regions that

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interact with the hippocampus in the context of punishment and/or reward to evoke these behavioral effects.

Important questions about the neural circuitry responsible for the renewal of a conditional fear response subsequent to extinction are addressed by **Wang, Jin, & Maren** using immediate early gene activity mapping in adult rats. The objective here was to determine whether or not neurons in ventral hippocampus that project to prelimbic and infralimbic regions of the medial PFC make dissociable contributions to renewal. That this might be the case is suggested by findings that link prelimbic and infralimbic cortex, respectively, with expression or suppression of conditional fear responses following extinction. In contrast to what might be expected, c-Fos expression in ventral hippocampal neurons was evident during renewal regardless of the medial PFC target. This outcome provides new insight into network interactions of renewal, and suggests that subpopulations of ventral hippocampus neurons either drive responses in medial PFC up (prelimbic cortex) or inhibit them (infralimbic cortex) with the same end result – renewal of the conditional fear response.

Next, we have three functional MRI investigations that examine the impact of emotional associates or affective context on learning, memory, and network connections with the hippocampus. In the first study, **Berkers, Klumpers, & Fernandez** had participants attempt to encode face-occupation pairs. Subsequent memory for the general occupational categories of studied faces – negative (e.g., "criminal") or neutral (e.g., "runner") – was well-matched, but memory for specific occupational names was significantly reduced in the negative condition. These outcomes are consistent with past reports of reduced *associative* memory specificity when one item from a pair has negative valence. Activity differences during encoding were greater in medial PFC and reduced bilaterally in the hippocampus for negative, as compared to neutral pairs, and functional coupling of these regions was stronger in this condition. Follow-up correlational analyses indicating that increased medial PFC-hippocampal connectivity was associated with poorer occupation-specific recall performance in the negative condition. In short, engagement of the medial PFC-hippocampus circuit seems to regulate memory specificity – potential neural mechanisms for this effect are described in the manuscript.

The next investigation in this subset goes one step further, as it was designed to disambiguate brain networks that are engaged by punishment and reward motivation, respectively. **Murty, Labar, & Adcock** demonstrate that both encoding success and patterns of connectivity with the hippocampus are affected by the motivational valence of a primary task. Results from their study indicate that when participants attempt to maximize rewards, surprising (task-irrelevant) items are well-encoded, and activity differences are evident in the hippocampus. Conversely, when participants attempt to minimize punishment, surprising items are encoded no more effectively than control items, and activity differences are evident in parahippocampal cortex. Evaluation of background connectivity patterns using these regions as seeds indicated that functional coupling of the hippocampus with ventromedial PFC was greater in the rewarding context, whereas greater functional coupling of the parahippocampal cortex with orbitofrontal cortex and the anterior temporal lobe was evident in the punishment context. The authors conclude that the motivational context of an event drives biologically distinct learning states, which in turn guide adaptive behavior and give rise to different mnemonic outcomes.

The final paper in this trio provides readers with increasingly precise information about the behavioral and neuroanatomical underpinnings of reward-facilitated memory outcomes. **Loh, Kumaran, Koster, Berron, Dolan, & Duzel** report that the effect of a rewarding scene context on incidental memory for associated items is only evident when high demands are placed on the putative hippocampal function of pattern separation. In this study, participants were presented with two sets of scenes – one set characterized by considerable perceptual overlap/ambiguity and another with exemplars that were perceptually distinctive. From each set, one scene served as a rewarding context and the other as a neutral baseline. Incidental memory for objects superimposed on these scenes was only enhanced for the rewarding scene that was a close perceptual match to its counterpart. Results indicated that this reward-related mnemonic boost was associated with co-activation of the dentate gyrus/CA3 hippocampal subfield, which has been linked to the pattern separation process, and substantia nigra/ventral tegmental area (SN/VTA), a major source of dopamine in the brain and a key player in the processing of reward. Here, the authors propose that requirements for hippocampus-supported disambiguation of similar scene contexts engaged the hippocampus and enhanced the reward-based response in SN/VTA, which in turn resulted in more effective incidental encoding, a possibility that is compatible with recently reported neuroanatomical evidence for direct CA3-SN/VTA pathway (Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011).

As indicated above, functional coupling of the hippocampus with ventromedial PFC is evident when incidental encoding occurs in the context of reward incentives. **Ford & Kensinger** report increased coupling in the same set of structures when participants successfully retrieved previously encoded information and indicated, via subjective ratings, that the recovered memory representations had high levels of internal vividness (e.g., emotions experienced during encoding). A qualitatively different set of structures were coupled with hippocampus (e.g. lateral temporal lobe) when ratings indicated that retrieval was characterized by recovery of high levels of external (e.g., perceptual) vividness. Identification of dissociable hippocampus-coupled networks as a function of qualitative differences in the kinds of detail that accompany retrieval is an important new finding because detail recovery has been treated as a unitary construct (e.g. the experience of conscious recollection) in the literature. The current investigation indicates that the kind of detail recovered during a retrieval task matters, and should be considered in future work.

Two more studies report functional coupling of the hippocampus with medial PFC – both of these studies point to a role for this circuit in the updating of existing knowledge with new information (i.e. the process of memory integration). **Schlichting & Preston** examined the dependence of this process – memory integration – on medial PFC-hippocampus coupling during active encoding and passive rest periods. In this experiment, during fMRI scanning, participants learned two sets of associates (B-C associates and X-Y associates). One item from each B-C pair overlapped with previously encoded content (A-B), providing opportunities for memory integration (A-C). Relative to the no-overlap control condition, encoding of B-C pairs elicited greater functional coupling between medial PFC and hippocampus, and with a specialized perceptual processing site (i.e. fusiform face area). Similar recruitment patterns were evident during a post-encoding rest phase. Results indicated that this coupling was greatest when encoded pairs were successfully integrated with previous knowledge, and that the strength of coupling was greatest for participants who performed best on a test of memory integration administered after scanning. Consistent with these observations performance on the test of memory integration was also positively correlated with white matter coherence in the pathways that connect these regions. Critically, these results indicate that the medial PFC-hippocampus circuit, together with specialized perceptual processing sites support integration processes that permit memory updating not only when integration might most likely occur (i.e. during encoding), but also during subsequent rest periods.

Increased hippocampus-ventromedial PFC coupling is also reported by **DuBrow & Davachi**, but here, this circuit is engaged when participants successfully recall the temporal order of within-context events. This fMRI study identifies the encoding correlates of successful subsequent serial recall within and across event boundaries, where "events" were disambiguated by virtue of category membership – faces or objects. Serial recall was better within the confines of a particular category than across event boundaries (e.g., transition from a faces to objects). Univariate contrasts indicated that accurate cross-boundary serial recall was associated with activity in the hippocampus and ventrolateral PFC – recruitment that may either reflect differences in the strength of encoding required to bridge the gap across event boundaries, or alternatively, the requirement to retrieve pre-boundary information, which is no longer in the focus of attention. No univariate activity differences were identified for within-category serial recall; instead, success here was correlated with functional coupling between hippocampus and ventromedial PFC. Consistent with conclusions drawn by Schlichting & Preston it is proposed that this effect may occur as a consequence of requirements to integrate new exemplars into the currently active context. These results extend the proposed medial PFC-hippocampus mediated integration processes to the domain of temporal order.

Evidence for functional coupling between the hippocampus and ventral visual processing sites (i.e. FFA) was reported by Schlichting & Preston. The next paper in this special issue examines background connectivity between ventral visual processing sites and MTL structures that provide the hippocampus with its input, but here, connectivity patterns are examined in the context of task-based attentional demands. **Córdova & Turk-Browne** presented participants with overlapping semi-transparent pictures of faces and houses, with instructions to attend selectively to one or the other in service of identifying 1-back repetitions. Especially compelling was the observation that the same voxels in ventral visual cortex, those with no preference for one category over the other, change their connectivity profiles with peririhinal cortex and parahippocampal cortex depending on the attentional demands of the task. For example, when faces were attended these ventral temporal voxels, which did not show category-specificity, were functionally coupled with peririhinal cortex; the connectivity pattern changed when houses were attended. This flexible shift between parahippocampal and peririhinal pathways is likely to be mediated by top-down control processes and may ultimately determine how downstream information is processed. While sources of this top-down control, contributions of the hippocampus to attentional processing constraints, and effects on subsequent memory remain to be elucidated, this work provide important new insights into the contributions of MTL structures to attention.

The final empirical paper in this special issue investigates whole-brain intrinsic functional connectivity with subregions of the parahippocampal gyrus and the hippocampus. This work, reported by **Wang, Ritchey, Libby, & Ranganath** extends recent observations that the peririhinal and parahippocampal cortices show dissociable patterns of intrinsic functional connectivity with anterior-temporal and posterior-medial cortical sites. Here, slices along the long axes of the parahippocampal gyrus and the hippocampus were grouped based on their shared connectivity patterns using a hierarchical clustering algorithm. Results revealed a new subregion of peririhinal cortex, distinct from the previously identified anterior-temporal network, with an activity pattern that correlated preferentially with auditory and visceral processing sites. A functional imaging task confirmed that task-based activity differences in all three parahippocampal gyrus subregions were dissociable. Strong dissociations in intrinsic connectivity patterns with subregions of the hippocampus were not identified in this study, but the investigators indicate that the combined use of resting state data and the slice-based parcellation may be insufficiently sensitive to such differences. It is suggested by the authors that the evaluation of intrinsic connectivity patterns with specific hippocampal subfields might be more effective. This work represents an important extension of the recently proposed PMAT framework (Ranganath & Ritchey, 2012), and opens the door for future research that could more effectively identify differences in connectivity patterns with subregions of the hippocampus.

The final four papers in this special issue are comprehensive research reviews that provide additional insights into network interactions with the hippocampus across a range of populations, procedures, and tasks. The first review, written by **Meister & Buffalo** tackles questions about how the hippocampus interacts with the oculomotor system to guide eye movement behavior. In a thorough treatment of the literature, the authors summarize findings that point to a role for memory in shaping eye movement behavior, along with evidence illustrating the dependence of these effects on the hippocampus. On the flip side, research findings are reviewed that indicate eye movement behavior can affect neural signals in the hippocampus. As the authors point out, there are considerable gaps in this literature that remain to be investigated. For example, by what neural routes does processing in the hippocampus affect the spatial distribution and time-course of eye movements? In other words, how does the hippocampus communicate with brain areas that control oculomotor behavior? Furthermore, is the hippocampus, which has been largely neglected in the oculomotor literature, uniquely capable of guiding eye movements that depend on allocentric, rather than retinotopic, representations of space? In short, the authors make a compelling case for further investigation into these systems level interactions along with several suggestions about how this work might proceed.

The next paper combines a meticulous review of retrieval suppression research with a compelling analysis of the potential neural mechanisms that may play a key role in this process. Two anatomical pathways are identified that, as described by **Anderson, Bunce, & Barbas**, could mediate inhibitory dorsolateral PFC-hippocampus interactions that are hypothesized to drive retrieval of once learned associates down following active suppression. In short, it is proposed that DLPFC, which does not project directly to the hippocampus, inhibits processing by virtue of its connectivity to the anterior cingulate (ACC), the thalamic reuiens nucleus, or both. The mechanisms of action in each case would be different, as ACC is positioned to inhibit hippocampus input and output by virtue of its inhibitory connectivity with rhinal cortex; in contrast, direct corrections mean that the nucleus reuiens could inhibit the hippocampus directly. The feasibility of these claims are given due anatomical consideration and points at which the neuroanatomical findings (from the non-human primate and rodent literatures) diverge is clearly articulated. This is a notable example of how effectively the human neuroimaging and the non-human animal literatures can coalesce to yield important new insights into network interactions with the hippocampus that affect learning and memory.

As described in several of the papers published in this special issue, the effectiveness of memory encoding and retrieval can be driven up or down by a variety of cognitive processes (e.g. emotion, retrieval suppression). However, it is also the case that memory can be modulated artificially by virtue of brain stimulation techniques. **Kim, Ekstrom, and Tandon** provide a timely overview of invasive and non-invasive methods that are being used to systematically manipulate memory performance. Consistent with vast network connectivity in the brain, studies that target distant brain structures, superficially at the skull, can impact the effectiveness of learning and memory processes that are mediated by the hippocampus. Studies that report improvements and deficits in memory are considered and the authors emphasize the importance of considering network dynamics in stimulation studies meant to target a specific brain region. The importance of this point was illustrated early on in this issue by Meng et al. who report considerable reorganization of the standard working memory network following neonatal hippocampal lesions in monkeys. Finally, a proposal is made by the authors about how neurostimulation techniques might be most effectively used in service of declarative memory modulation.

The final article, by **McKenzie and colleagues,** describes observed commonalities and discontinuities in how memory is organized across a set of connected structures – rhinal cortices, hippocampus, and PFC – and a model is proposed that capitalizes on this anatomical connectivity and the representational properties of these structures. Furthermore, the authors provide a compelling rationale in favor of analyses that focus on neural populations, rather than single units, to better elucidate the complexity of experience that is characteristic of episodic memory. Considered in the broader context of this special issue, it becomes clear that the proposed model makes important in-roads with several of the empirical studies (e.g. those that evaluate the impact of emotion on memory, those that address questions about the neural substrates of memory integration). This work, along with the other valuable contributions from the authors involved in this special issue of NLM, clearly demonstrates the importance of thinking about processes that have been traditionally identified with the hippocampus and MTL within the context of network level interactions with multiple brain areas. We hope that the collection of papers presented here will help to move the field forward in this direction.

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Deborah E. Hannula
Fred J. Helmstetter

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