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COMMENTARY

The Hippocampal Indexing Theory and Episodic Memory: Updating the Index

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ABSTRACT: A little over 20 years ago, (Teyler and DiScenna, 1986; Behav Neurosci 100:147–152) proposed the hippocampal memory index theory. It offered an account of episodic memory based on the intrinsic organization of the hippocampus, its synaptic physiology and its anatomical relationship to other regions of the brain. The essence of their idea was that the hippocampus was functionally designed and anatomically situated to capture information about neocortical activity generated by the individual features of behavioral episode. Moreover, because the hippocampus projects back to these neocortical regions the information it stored could serve as an index to the pattern of neocortical activity produced by the episode. Consequently, a partial cue that activated the index could activate the neocortical patterns and thus retrieve the memory of the episode. In this article we revisit and update indexing theory. Our conclusion is that it has aged very well. Its core ideas can be seen in many contemporary theories and there is a wealth of data that support this conceptual framework. © 2007 Wiley-Liss, Inc.

KEY WORDS: pattern completion; pattern separation; episodic memory

In the mid 1980s, a series of articles by Teyler and DiScenna (1984a,b, 1985) appeared that culminated in what is the hippocampal memory indexing theory (Teyler and DiScenna, 1986). This theory was intended to provide an in principle account of the contribution of the hippocampus to the storage and retrieval of experiences that make up our daily lives. In essence it was a theory of how the hippocampus contributes to episodic memory. As such it was a theory about (a) the role of the hippocampus in memory formation, (b) the nature of the memory trace, and (c) memory retrieval. In addition, because of how indexing theory viewed the nature of connections between the hippocampus and the neocortex, it also provided a rationale for speculating about how the initial memory representation might change with age and repetition.

Since that time other theories encompassing many of the same ideas have appeared. Moreover, there now exists an extensive literature that is relevant to the basic assumptions of the indexing theory. Thus, in our view the time is right to consider how well the earlier ideas have survived the test of time. The purpose of this article is to provide such an assessment.

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In overview indexing theory can be understood in relationship to Figure 1. The theory assumes that the individual features that make up a particular episode establish a memory trace by activating patterns of neocortical activity. This pattern of activity projects to the hippocampus (Fig. 1B). As a consequence, synapses in the hippocampus responding to the neocortical inputs and synapses connecting the set of coactivated hippocampus neurons are strengthened. The outcome of this neocortical -hippocampus interaction is the memory trace represented in Figure 1C. Note that the experience is represented simply as the set of strengthened synapses in the hippocampus that result from the input pattern. There are no modifications among the neocortical activity patterns. Thus, the memory trace is a hippocampus representation of cooccurring patterns of activity in the neocortex.

The "indexing" nature of the memory trace can be illustrated in relationship to memory retrieval. Note in Figure 1D a subset of the original input pattern is received by the neocortex. The projections from these input patterns activate the connected neurons in the hippocampus representing the original experience. The activation of this representation then projects back to the neocortex to activate the pattern representing the entire experience (Fig. 1E). It is this projection back to the neocortex that conveys the indexing property to the hippocampus representation. In this framework, the hippocampus itself does not contain the content of an experience but it does provide an index that allows the content to be retrieved.

Teyler and DiScenna noted that structure of the initial memory trace, in principle, allows for continuous interaction between the hippocampus representation and the neocortical patterns that it indexes. Thus, they speculated that, as a result of repeated activation of the index, either by direct activation, reinstatement or replay during sleep, the connections among the neocortical activity patterns might be gradually strengthened. So, in principle the retrieval of the memory might no longer have to go through the hippocampal index (see Fig. 1). Thus, it is possible that the role of the hippocampus in retrieving a particular memory might be temporary (see also Marr, 1971; Squire et al., 1984).

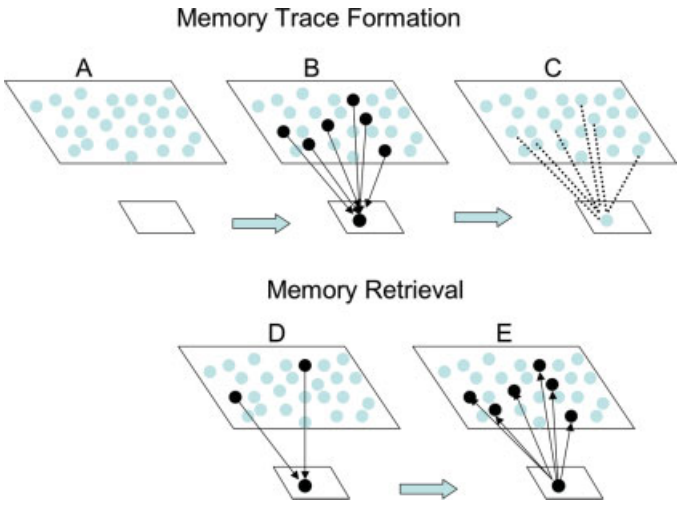

FIGURE 1. Memory Formation: (A) The larger top layer represents potential patterns of neocortical activity; the smaller bottom layer represents the hippocampus. (B) A set of neocortical patterns activated by a particular experience projects to the hippocampus and activates a unique set of synapses. (C) The memory for the experiences is stored as strengthened connections among those hippocampal synapse activated by the input pattern. Memory retrieval: (D) A subset of the initial input pattern can activate the hippocampal representation. (E) When this occurs output from the hippocampus projects back to the neocortex to activate the entire pattern. Thus the hippocampus stores an index to neocortical patterns that can be used to retrieve the memory. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

HISTORICAL CONTEXT

Indexing theory was initially conceived as a way of integrating three important emerging literatures. Brenda Milner's analysis of HM strongly suggested that the hippocampus was part of a neural system that maintains some record of the events of our lives (Milner, 1959, 1970; Scoville and Milner, 1957). HM, for example, was capable of learning a motor task, yet was unable to recall the training session that produced the learning. Nor could he remember interacting with the experimenters. The phenomenon of long-term potentiation (LTP) had been discovered and received extensive investigation as a neuronal mechanism that might support information storage. In addition much of the topological anatomy of the hippocampus was known, and its anatomical connections with other regions of the brain were beginning to emerge.

At the time indexing theory was proposed the concept of multiple memory systems was beginning to gain favor among both neurobiologists and psychologists. The multiple memory systems idea emphasized that memory was not supported by a monolithic system but instead that the brain contains specialized systems that are designed to store and utilize the different kinds of information contained in our experiences (see Sherry and Schacter, 1987; Schacter and Tulving, 1994). In the ensuing years a variety of taxonomies were proposed to differentiate the special contribution of the hippocampus from extrahippocampus systems. They include the locale versus taxon system (O'Keefe and Nadel, 1978), memories versus habit systems (Mishkin and Petri, 1984), configural versus simple association systems (Sutherland and Rudy, 1989), relational versus nonrelational (Cohen and Eichenbaum, 1993; Eichenbaum, 1994), and the declarative versus nondeclarative systems (Cohen, 1981; Squire, 1992). These taxonomies were all predicated on the fact that damage to the hippocampus does not impair performance on all memory dependent tasks but instead results in a pattern of spared and impaired performance.

INDEXING THEORY AND EPISODIC MEMORY

Indexing theory was not explicitly couched in a multiple memory framework. Instead it was offered to explain the obvious impairment presented by HM. After his surgery he could not recall the events or episodes of his life. Teyler and DiScenna used the term experiential memory to capture what was lost. In the current context the theory was about how the hippocampus supports what Tulving (1983) calls episodic memory. In retrospect this was a good choice. There has been much debate about the utility of some of the taxonomies; however, the idea that the hippocampus supports episodic memory has never been seriously questioned. Indeed, Tulving and Markowitsch (1998) proposed that it is just episodic memory that depends on the hippocampus.

Some Attributes of Episodic Memory

Unfortunately, Tulving and Markowitsch (1998) chose to ignore the great similarity of the anatomy and physiology of the rodent and nonhuman primate brains to the human brain (see Eichenbaum, 2000) and proposed a set of attributes that would exclude the possibility that animals other than people could have episodic memories. In fact, they dismissed this possibility outright. It is useful, however, to discuss more commonly accepted attributes of memory that an episodic memory system should provide.

Episodic content

By definition the content of episodic memory is episodic. This means that the system is designed to capture information about single episodes of our lives. What constitutes the duration of an episode is vague. However, the gist of this idea is the system can capture information about an experience that only occurs once. It has been suggested that every episode of our lives is unique, even if it contains highly overlapping information (see Nadel and Moscovitch, 1997). Thus, we can remember many different instances of practicing the piano or driving our car to the same parking lot.

Automatically captures information

The episodic memory system automatically captures information simply as a consequence of our exploring and experiencing the environment. Under normal circumstances the epi-

sodic memory system is always "online" capturing information about the various experiences that make up our day and it is doing so without intention on our part.

Supports conscious recollection

Perhaps at the center of the episodic memory system is that it can support our conscious recollection of previous experiences. The term conscious recollection has two meanings:

1. It means *intentional* in the sense that one can actively initiate a memory search. In this case the reference would be to the manner in which retrieval is initiated.
2. It also means that you have an *awareness* of remembering - a sense that a memory trace has been successfully activated. In this case the reference would be to a subjective feeling that is a product of the retrieval process (Schacter, 1987).

Animals other than people cannot provide verbal responses to memory question or their subjective awareness. Thus, we currently do not have and may never have any way of knowing if animals other than people have the ability to consciously recollect. This property has always been a significant barrier to establishing an animal model of episodic memory. However, it is possible that the subjective state of conscious awareness that we have successfully remembered some event may be associated with the content of the memory trace. A number of researchers agree that the feeling of remembering emerges when a retrieved memory trace contains information about the time, place, or context of the experience that established the memory (e.g., Nadel and Moscovitch, 1997; Squire and Kandel, 1999). In describing the importance of contextual information to recollection, for example, Squire and Kandel (2000, page 69) wrote,

"Once the context is reconstructed, it may seem surprising how easy it is to recall the scene and what took place. In this way, one can become immersed in sustained recollection, sometimes accompanied by strong emotions and by a compelling sense of personal familiarity with what is remembered."

While it may not be possible to determine that nonhumans experience the subjective state of conscious awareness, it is possible to determine that they store many of the attributes that define the time or place of an experience. We will return to these attributes after we review the anatomy and physiology of the hippocampus and its related cortices.

UNDERSTANDING EPISODIC MEMORY FROM INSIDE TO OUTSIDE

Indexing theory was developed to explain why episodic memory depends critically on the hippocampus. It is generally agreed that experience is stored in networks of neurons by experience-induced neural activity strengthening or weakening synaptic connections linking members on the network. There is, however, uncertainty about where episodic memory is stored, how it is maintained, and how it is accessed. Teyler and DiScenna were motivated to show how the answers to such questions about episodic memory fall naturally out of a basic understanding of the: (a) anatomical connections of the hippocampus to other brain regions, (b) intrinsic connections within the hippocampal complex, and (c) synaptic plasticity properties of the hippocampus and the neocortical regions to which it relates. In this sense it was an attempt to build a theory of memory starting with what was known about the brain as opposed to mapping psychological theories of memory on to the brain.

As noted, indexing theory proposes that the content of our experiences is stored in the multiple neocortical loci activated by experience and the hippocampus stores an index of those neocortical loci. The index is established quickly via mechanisms that support LTP (and long-term depression, LTD) in the hippocampus. Experience-driven changes in connections among neocortical loci require more repetition. In the following sections, with an eye toward some updating, we will describe how the anatomy and physiology of the hippocampus and neocortex can provide the biological basis of the indexing theory and episodic memory.

Neocortex Anatomy and Information Processing

In the present context we emphasize two organizing principles of neocortical anatomy. One principle relates to the semihierarchical flow of information between neocortical areas; the other principle relates to the local columnar organization of the functional units within the specific areas of neocortex.

The semihierarchical organization of the neocortex

Sensory information from which episodic memories is derived occurs in the primary sensory areas of cortex. The numerous supplemental sensory areas operate in series (each being the source of information for the next area) and in parallel (all receiving sensory input from the thalamus). The supplementary sensory areas provide additional processing of the raw sensory data and, in turn, project to other areas termed "association areas" that receive multi-modal information from different sensory modalities. In this semihierarchical, series-parallel scheme each sensory area extracts different aspects of sensation, but all areas possess a map of the relevant sensory receptor (retina, cochlea, etc). Indeed, an organizing principle of neocortex is that it maps something onto its surface, be it body surface, retina, tongue, or muscles. While we know much about what is mapped onto sensory and motor cortex, we know much less about what is mapped onto polymodal association areas. However, ultimately information processed through these neocortical regions converges onto the hippocampus (see Fig. 2).

Columnar organization of neocortex

A second organizing principle of neocortex is that all of the cortex is composed of vertically oriented (e.g., from white matter to pial surface six-layered columns about 0.5 mm in diameter). Columns are the basic processing unit of the neocortex. A column consists of about 10,000 pyramidal cells and numerous interneurons, all richly interconnected, through which ascend

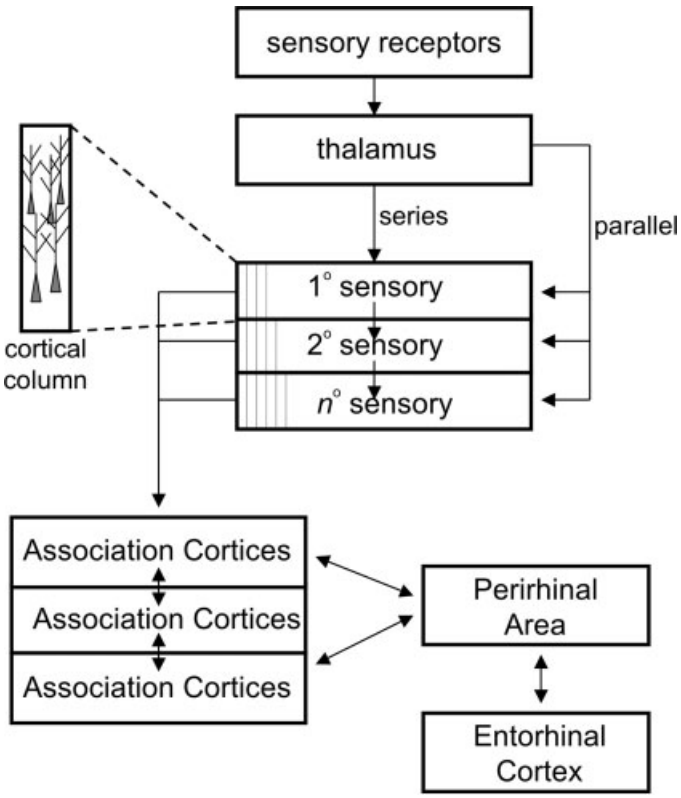

FIGURE 2. Sensory information from which episodic memories is derived occurs in the primary sensory areas of cortex. The supplemental sensory areas operate in series and in parallel. The supplementary sensory areas provide additional processing of the raw sensory data and, in turn, project to association areas that receive multi-modal information from different sensory modalities. In this semihierarchical, series-parallel scheme each sensory area extracts different aspects of sensation. Ultimately information processed through these neocortical regions converges onto the hippocampus.

thalamic input for processing and subsequent transmission to other modules or subcortical areas (Bannister, 2005). Columns communicate with their neighbors but can be thought of functionally as individual processors. In sensory neocortex all the neurons in a column possess the same receptive field and response specificity with respect to one quality of the sensory modality (light touch, for instance). However, the receptive fields become larger and the specificity more become complex as one goes from primary to supplementary sensory areas. In association areas, where our knowledge is far more limited, they appear to be responding to complex objects, consistent with the idea that they are integrating input from many less complex columns (Lavenex and Amaral, 2000).

Indexing theory assumes that incoming multi-modal sensory information is processed in a distributed array of neocortical modules that, acting together, result in the sensation and perception of episodic information. Since the complex sensory information derived from episodic experience is processed in many widely scattered cortical modules, linking them together to form a unified perception of experience creates what is known as the "binding problem." Unique synchronous oscillations (gamma oscillations) that have been observed in widespread cortical areas might provide the physiological basis for binding the areas into a functional unit (Melloni et al., 2007).

Hippocampus Anatomy and the Information Processing Loop

The hippocampal formation complex is anatomically simpler than neocortex and is usually considered to comprise the dentate gyrus (DG), the hippocampus proper (areas CA1–(3)), and the subiculum. Each bilaterally symmetrical hippocampus consists of two interlocking sheets of neurons and, in rodent, somewhat resemble a cashew nut. These sheets of densely packed and aligned neurons receive laminated en-passage inputs from neocortical association areas and subcortical regions, and from contralateral and ipsilateral hippocampus.

The entorhinal cortex (EC) and closely related association cortices bring highly processed information to the hippocampus complex (see Fig. 3). More specifically, entorhinal efferents from layer II make excitatory synapses onto granule cells of the DG and pyramidal cells of area CA3, whereas layer III outputs synapse in CA1 and subiculum. The EC, in turn, receives its input from perirhinal cortical areas, prefrontal neocortex, and association cortices - thereby receiving highly processed information from neocortex. The EC has reciprocal outputs to the areas from which it receives inputs. The hippocampus also receives subcortical input from numerous sources including amygdala, thalamus, medial septum, raphe nuclei, and locus coeruleus.

Each hippocampus also receives a large commissural input from the contralateral hippocampus, as well as an ipsilateral associational input. Within the hippocampus information processing generally proceeds from DG > CA3 > CA1 > subiculum, with additional inputs and outputs at each stage. The main hippocampus outputs are return projections to the EC and to the cortices that provide input to the EC, and to the septal area, thalamus, and the other subcortical areas supplying afferents to hippocampus. Swanson has emphasized (Swanson and Mogenson, 1981) that the "key to understanding the function" of the hippocampus resides in its connectivity with neocortex and subcortical areas. Following Swanson's lead, indexing theory assumes that the hippocampus is positioned to integrate the information contained in these subcortical visceral inputs with the more "cognitive" inputs from neocortex.

The central assumption of indexing theory is that experience generates an index in the hippocampus that encodes locations in cortical space. Thus, if the index is activated it will activate the relevant patterns of activity in neocortical space. To do this requires: (a) reciprocal pathways connecting hippocampus and neocortex, (b) topological specificity between the two regions that allows neocortex to be mapped onto hippocampus, and (c) modifiable synaptic connections linking neocortical and hippocampus neurons that can encode and maintain the neocortical-hippocampus relationships established by the episode. In other word input patterns from neocortical regions must activate neurons in the hippocampus and synaptic connections linking these neocortex patterns to hippocampus must be strengthened.

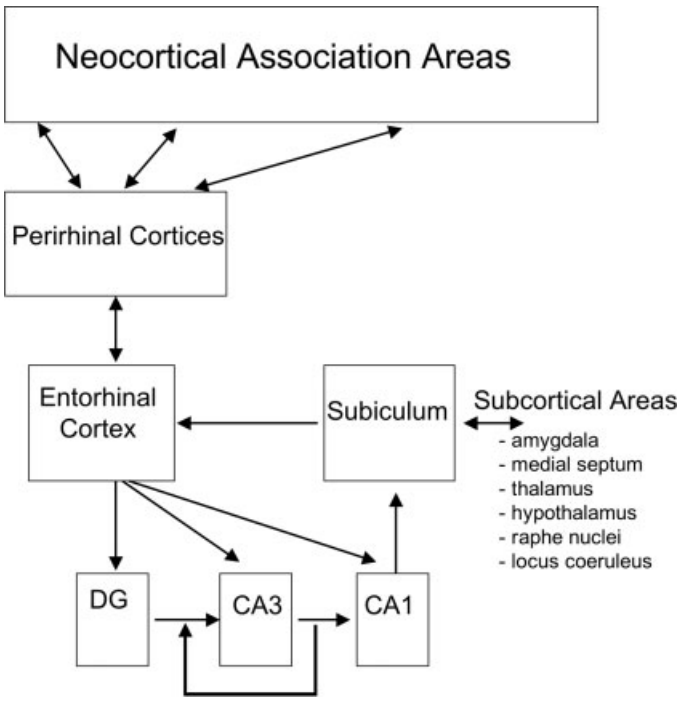

FIGURE 3. The EC brings highly processed information to the hippocampus. The EC, in turn, receives its input from perirhinal cortical areas and association cortices - thereby receiving highly processed information from neocortex. The hippocampus also receives subcortical input from numerous sources including amygdala, thalamus, medial septum, raphe nuclei, and locus coeruleus. The hippocampus also receives a large commissural input from the contralateral hippocampus, as well as an ipsilateral associational input. Within the hippocampus information processing generally proceeds from DG > CA3 > CA1 > subiculum, with additional inputs and outputs at each stage. The main hippocampal outputs are return projections to the EC and to the cortices that provide input to the EC, and to the septal area, thalamus, and the other subcortical areas supplying afferents to hippocampus. Indexing theory assumes that the hippocampus is positioned to integrate the information contained in the subcortical visceral inputs with the more cognitive inputs from neocortex.

The existence of reciprocal connectivity between hippocampus and its cortical inputs has been demonstrated for the claustrum (Berger et al., 1981), cingulate gyrus (Vogt and Miller, 1983), and EC (Burwell et al., 2004; Chrobak et al., 2000). Moreover, Amaral (Lavenex and Amaral, 2000) argues that entorhinal, perirhinal, and parahippocampal cortex function as part of a hierarchy of associational cortices, such that only highly processed information reaches the HPC. In such a hierarchy their extensive reciprocal connectivity to hippocampus is replicated in their connectivity with neocortex. Thus, it appears that the hippocampus can access all neocortex via a hierarchy of reciprocally interconnected association cortices.

Mechanisms of Synaptic Plasticity in Hippocampus and Neocortex

To create and maintain an index, the connections linking neocortical projections to the hippocampus must be modifiable. When indexing theory was initially proposed, it capitalized on the fact that in both intact organisms (Bliss and Lomo, 1973) and in slices taken from the hippocampus (Teyler, 1999) synapses in different regions of the hippocampus could be modified by synaptic activity. Thus, not only does the hippocampus see what is happening in the neocortex and subcortical regions, the mechanism supporting synaptic plasticity are available to support an index. During the intervening period research on hippocampus and neocortical synaptic plasticity has exploded beyond what can be reasonably summarized in this article. Thus, in the next sections we present a few caveats and general principles that are relevant to creating an index.

Indexing theory embraced the assumption that most of our daily experiences are insignificant and that it would be wasteful to devote the energy needed to strengthen and sustain connections among patterns of activity generated in neocortical modules. This assumption implies that the mechanisms supporting synaptic plasticity in the hippocampus and neocortex will differ. Specifically, synaptic connections in the hippocampus should be more labile and easily modified than those linking neocortical modules. We will highlight some of the research in the intervening period that supports this assumption.

Pyramidal neurons are the principle cell type and glutamate is the principle excitatory neurotransmitter in both the hippocampus and neocortex. Glutamatergic afferents in both regions synapse upon dendritic spines, and synaptic activity can increase (as measured by LTP) or decrease (as measured by LTD) the strength of these synapses. Much of what is known about the mechanisms of LTP/LTD comes from research in the CA1 area of hippocampus. However, it is important to recognize that other synapses, even within the hippocampal formation, utilize somewhat different mechanisms of action (Abraham and Williams, 2003). Although the cellular mechanisms vary, the fundamental idea is that synaptic activity alone can modify synaptic strength. We will focus on several key properties of synaptic plasticity in both the hippocampus and neocortex rather than the details of its cellular mechanisms of action.

Indexing theory requires that synapses in the hippocampus can be rapidly and reversibly strengthened, whereas synapse linking neocortical modules require more input but support more stable changes. There are in fact different forms of LTP that vary according to their durability, and their requirements for induction (Malenka and Bear, 2004; Raymond, 2007) might serve to satisfy the requirements of indexing theory.

An important general finding is that there is a strong positive relationship between the intensity of the stimulus used to induce LTP and its duration. Moreover, this relationship depends on the ability of the induction stimulus to engage different sources of extracellular and intracellular calcium (Raymond and Redman, 2002, 2006; Raymond, 2007). Relatively modest levels of afferent input (and thus a modest amount of postsynaptic depolarization) will engage the familiar NMDA-receptor dependent Ca^{2+} influx (Collingridge et al., 1983) and rapidly induce a form of LTP that can be reversed (depotentiated) by low-frequency afferent activity (Wagner and Alger,

1996). This rapidly induced NMDA-dependent LTP is an excellent candidate for rapidly generating an index.

In contrast the most enduring form of LTP requires a greater level of afferent input, one that is sufficient to significantly increase the extent to which the neuron depolarizes. Under these conditions extracellular Ca^{2+} enters the cell via voltage dependent calcium channels (VDCCs). LTP supported by this mechanism develops more slowly but is much more stable (Grover and Teyler, 1990; Moosmang et al., 2005; Raymond, 2007). Thus, due to its more demanding induction requirements and stability, VDCC-dependent LTP is a candidate for strengthening connections among coactive ensembles of neocortical neurons.

One potential problem with the earlier analysis is that both NMDA-dependent and VDCC-dependent LTP can be found in both hippocampus and neocortex. Moreover, one should expect that experiences that establish episodic memories would produce modest levels of activity in both the neocortex and hippocampus. Thus, for our view to hold there should be mechanisms operating in the cortex to limit the induction of the easily induced NMDA-dependent form of LTP. This appears to be the case because in vivo studies clearly show that it is more difficult to induce LTP in cortical synapse that in the hippocampus. How might this happen? One possibility is that strong inhibitory control mechanisms are present in the neocortex that prevents the requisite depolarization from developing (Werk and Chapman, 2003).

We have emphasized that conditions in the hippocampus favor the rapid induction of a reversible form of LTP and that would initially support the index. However, the voltage dependent calcium mechanisms needed to generate an enduring index are also present in the hippocampus (see Morgan and Teyler, 1999; Raymond and Redman, 2002, 2006; Raymond, 2007) and could come into play if the episode is repeated. Similarly, alterations in neuromodulatory activity associated with reward have been shown to influence the induction and expression of LTP (Otmakhova and Lisman, 1996; van der Zee and Luiten, 1999; Straube and Frey, 2003), suggesting that the emotional significance of the episode can also play a role.

The mechanism engaged by repetition and the neuromodulatory activity associated with rewards can also ultimately result in strengthening connections among neocortical modules activated by the experience. Note such experiences would have the parallel effect of producing an enduring index and strengthening connections among ensembles of neurons in the relevant neocortical modules. Strengthening connections among ensembles of neocortical neurons may also be associated with high frequency activity associated with perceptual binding (Melloni et al., 2007) and bursts of activity during sleep (Battaglia et al., 2004; Behrens et al., 2005). Both forms of increased high frequency discharge have been observed in task-appropriate areas of neocortex and hippocampus, and both are candidates for the process linking together the hippocampal index and the neocortical ensemble.

This brief review suggests that the features of synaptic plasticity in hippocampus and neocortex are different. Mechanisms available in the hippocampus can support both a rapidly induced but transient index and indexes that can endure for long periods of time. In contrast, it is possible to strengthen connections among cortical neurons that endure, but the supporting mechanisms require stronger levels of afferent input. We close this section with the caveat that while compelling, this scenario is undoubtedly incomplete and oversimplified. Our emerging understanding indicates a great deal of complexity and regional heterogeneity in neocortical circuitry and plasticity (Ismailov et al., 2004; Hardingham and Fox, 2006; Sjostrom et al., 2007). Just as there are cortical networks specialized for different aspects of perception, there may be mnemonic networks specialized for different types of memory storage.

FUNCTIONAL PROPERTIES OF THE INDEX

The intrinsic organization of the hippocampus, its synaptic physiology and anatomical connections with the neocortex provide the neurobiological foundation for episodic memory. In this section some of the functional properties of this system as they relate to memory storage and retrieval will be highlighted.

The Hippocampal Index – A Memory Trace With No Content

As noted, like Marr's theory (1971), indexing theory was predicated on the belief that much of what we experience is of no lasting significance. Thus, there is no need to automatically strengthen connections among patterns of activity generated in neocortical modules. The hippocampal index provides a quick and relatively inexpensive way to access the content of an episode. The content of experiences is registered in the neocortical modules and the plasticity properties of the hippocampus allow it to rapidly and economically bind neocortical inputs into an index that can temporarily access those sites. Thus, rather than strengthening connections among the neocortical modules that represent the content of an experience, projections from neocortical sites are rapidly and economically bound into an index in the hippocampus. If the information is of no particular importance then either by natural degradation of these easily acquired connections (decay of LTP) or by interference produced by other stimulus inputs (depotentiation), the index will be lost. However, if the content of the experience is significant and/or repeated the index will be resistant to decay.

Ironically, the caveat in this scenario is that no content is being stored in hippocampus. The memory trace is the index. The hippocampus has neither the computing power nor functional organization to accomplish the analytical processing done by neocortex - so it contains no content. The content resides in the neocortex.

Indexing Theory, Pattern Completion, and Pattern Separation

We have provided a general description of indexing theory and the neurobiology on which it stands. There are two impor-

tant concepts that need to be further discussed in relationship to indexing theory–the related concepts of *pattern completion* and *pattern separation*. Understanding these concepts is central to understanding how the index retrieves an episodic memory.

A subset or portion of the experience that originally established the memory trace can activate or replay the entire experience. The process by which this happens is called pattern completion. It is the most fundamental process provided by the index (see Fig. 1). When neocortical activity patterns are produced by a subset of the elements of a prior episode, their projections to the hippocampus will activate the index and it will project back to neocortical units to activate the entire pattern of activity generated by the original episode.

Many theorists recognize the importance of pattern completion to the retrieval of episodic memories (e.g., Marr, 1971; McNaughton and Nadel, 1990; McNaughton, 1991; Squire, 1992; Rolls, 1996; O'Reilly and Rudy, 2001). Squire (1992) for example suggested that it is this process that makes the hippocampus central to conscious recall. Indexing theory made no attempt to provide a computational account of how information processed through the hippocampus actually performs these operations, but others have provided detailed accounts of how the different subfields of the hippocampus accomplish this task (see McNaughton and Morris, 1987; O'Reilly and Rudy, 2001; Rolls and Kesner, 2006). All of these theories assign special importance to CA3 because of the extensive CA3-CA3 connections that Marr called an autoassociative network (Marr, 1971). These connections enable it to associate the different sets of neurons in the hippocampus that respond to a specific pattern of neocortical input. Information processed through CA3 is fed forward through CA1 to EC.

In principle, the return projections from the hippocampus to the neocortex provide the basis for the index to support pattern completion. However, given that these projections must connect very broadly back to the sending areas, there is an obvious problem. How does the index activate precisely the same neocortical patterns that constituted the input of the episode? Why does not the hippocampus output activate all of the potential cortical units to which it projects? To achieve the required specificity needed to retrieve the memory there must be a selective strengthening of the outputs from the hippocampus back to the cortical patterns activated by the inputs. O'Reilly and Rudy (2001) suggested one way this could happen (Fig. 4). They assume that neocortical activation patterns come into hippocampus via the EC EC. The activation pattern present in EC generates two representations in the hippocampus. One representation is projected via the DG onto CA3 where the active units in CA3 are bound and create an index (O'Reilly and Rudy, 2001, called it a conjunctive representation). EC also projects directly to CA1 where the activated neurons create a second representation of the episode. Because the neurons in CA3 and CA1 representing the entorhinal input are coactive their synaptic connections are strengthened. It is the output of CA1 neurons that project back to EC. This means that during the encoding/memory formation stage there is the opportunity for connections from CA1 neurons and neurons representing the input pattern in EC to be selectively strengthened. Consequently, during memory retrieval a partial input from EC that is sufficient to activate the CA3 index would activate the CA1 representation that would in turn activate those specific patterns of activity representing the original input in the EC.

One of the remarkable aspects of the episodic memory system is that it has the capacity to maintain distinct representations of similar but separately occurring episodes. This property is called pattern separation. Thus, if two similar input patterns ABCD and CDEF are presented, the episodic memory system has the ability to store distinct representations. One of the major advantages of an index is that, provided the inputs do not extensively overlap, it can provide a way of separating overlapping episodes. This allows the appropriated patterns of neocortical activity to be activated during retrieval. In contrast, if only associative networks were available to link the neocortical modules activated by the similar inputs it would be difficult to keep them distinct. Thus, a subset of either pattern would activate the entire neocortical network that contains both the ABCD and CDEF patterns. The advantage of indexing over neocortical associative processes for remembered episodes is illustrated in Figure 5. Contemporary computational models recognized the importance of the pattern separation problem and believe it derives from the architecture by which large overlapping patterns of activity in neocortex converge onto a much smaller set of neurons in the hippocampus that might be randomly activated (see O'Reilly and McClelland, 1994; O'Reilly and Rudy, 2001 for a detailed argument).

What Neocortical Areas Are Being Indexed?

The original indexing theory suggested that the hippocampus directly indexed all areas of neocortex. Recent data from several laboratories (Chrobak et al., 2000; Burwell et al., 2004), however, suggests that this might be incorrect. Direct hippocampus-neocortex projections may be confined to the adjacent association cortices of the medial temporal lobe, specifically the entorhinal and related cortices. Moreover, one might argue that if the hippocampus is indexing all neocortical loci, then the greatly expanded human neocortex should have been accompanied by a correspondingly larger hippocampus. However, this did not occur. Aside from the general explosion in human neocortex, the other new development is the expansion of association areas. They are small in rat brain but pronounced in the human brain.

In rodent brain, the hippocampus communicates primarily with the entorhinal areas, which in turn communicate with the rest of neocortex. Thus instead of the hippocampus indexing all of neocortex, it is probable that it participates in a hierarchical indexing scheme whereby it indexes the association cortex (in rat, the entorhinal area), which then indexes the rest of neocortex. Since association areas assemble inputs from primary areas one can thus view the hippocampus as assembling inputs from the association cortex - an association cortex for the association cortex, if you will.

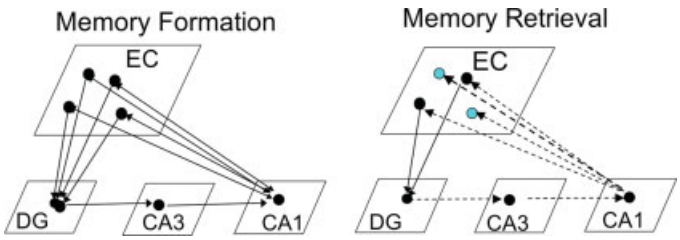

FIGURE 4. During memory formation the episode activates patterns of neural activity in EC that is projects via DG to CA3 where the index is created. EC also projects directly to CA1 where a second representation is created. Connections between the CA3 and CA1 representations of the EC input representation get strengthen. CA1 also projects back to EC. Synchronized coactivity of the CA1 neurons (activated by the EC projections) and the EC neurons (activated by the experience) provide the opportunity to selectively strengthen the CA1 projections to the EC input pattern. Consequently during retrieval a partial input pattern to CA3 can activate the CA1 representation that can then complete the original EC input. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

BEHAVIORAL EVALUATION OF INDEXING THEORY

When indexing theory was published there was little behavioral data available to assess it. The era of animal research immediately following Milner's analysis of HM's amnesia was notable primarily for demonstrating how well rodents could do without the hippocampus (see Douglas, 1967). Since its publication, however, there has been an explosion of research demonstrating the involvement of the hippocampus in a wide range of behavioral tasks both in rodents and primates. We do not intend to relate indexing theory to this vast literature (see O'Reilly and Rudy, 2001; Rolls and Kesner, 2006 for more comprehensive treatments; Morris, 2007). Our goal is more modest. It is to provide evidence that evaluates indexing theory in the domain to which it was intended to explain—episodic memory. Thus, we will be concerned only with relating the hippocampus to the properties of the episodic memory system that were described earlier. Indexing theory makes several claims that can now be evaluated.

- The hippocampus captures the context in which events are experienced.
- The hippocampus automatically captures context information.
- The hippocampus captures single episodes.
- The hippocampus supports pattern completion and separation.
- The hippocampus supports systems consolidation.

The Hippocampus and Context Representations

The idea that conscious recollection of an episode depends on the hippocampus is well established. People with significant damage to the hippocampus cannot consciously recollect. A large number of studies with rodents support the idea that the hippocampus is critical to this process.

The context preexposure paradigm developed by Fanselow (1990) provides a powerful tool to study context representations. It is based on a phenomenon called the immediate shock effect. If a rat is placed into a fear-conditioning chamber and shocked immediately (within 6 s), it will later show little or no fear of the conditioning chamber. However, if the rat is allowed to explore the conditioning chamber for a couple of minutes the day before it receives immediate shock, it will subsequently show substantial fear to that context. This enhanced fear to the context is believed to represent the fact that the rat acquired a representation of the context, because if the rat is preexposed to a different context than the one in which it was shocked and tested it shows not fear. Rats who are not preexposed to the shock/test context fail to show conditioned fear because they did not have time before the shock to acquire a representation of the context.

It is also the case that rats acquire a index-like representation of an explored context because exposing the animals to just the separated features that make up the context - such as floor texture, illumination, chamber shape, and ambient auditory cues, does not facilitate conditioning to a particular context. As indexing theory would suggest, the context preexposure effect requires that the rodent be exposed to the exact conjunction of stimulus features that make up the context in which the animal is shocked and tested (Rudy and O'Reilly, 1999, 2001). Acquiring an Index Representation of Context Requires the hippocampus because:

- Anterograde dorsal hippocampus lesions eliminate the preexposure effect (Rudy et al., 2002).
- Inactivating the dorsal or ventral hippocampus with muscimol before either (a) preexposure, (b) immediate shock, or (c) the test for context fear, greatly reduces the preexposure effect (Matus-Amat et al., 2004; Rudy and Matus-Amat, 2005; Rudy et al., 2004).
- Injecting the NMDA receptor antagonist D-AP5 into dorsal hippocampus before context preexposure, but not before immediate shock, greatly reduces the effect (Matus-Amat et al., in press)

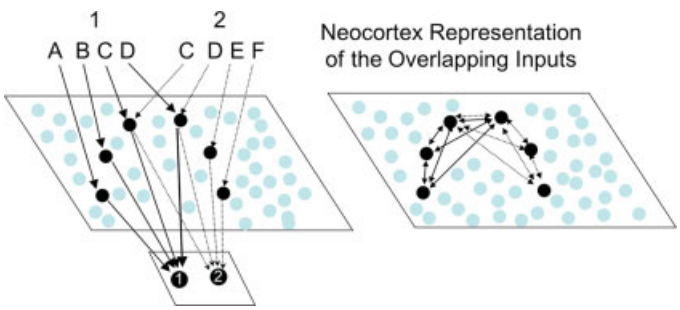

FIGURE 5. The hippocampus supports pattern separation by creating separate indexes to similar input patterns. Note that two similar input patterns (1:ABCD and 2:CDEF) converge on different representational units in the lower level that represents the hippocampus. In contrast these two patterns would not be separated in the neocortex, so it would have trouble keeping these patterns separated. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

These findings establish that rats can acquire an index representation of context that depends on the hippocampus.

The Index, Context, and Conscious Recollection

Conscious recollection of episodic memories depends on the hippocampus. Indexing theory assumes that conscious recollection derives, in part, from the index representation that binds components of the episode into representation of the context. Thus, encountering some component of the episode would activate the index that in turn would project back to the neocortex and activate the cortical ensembles of the context. This activation might provide a basis for conscious awareness (see Eichenbaum et al., 2007) for a similar analysis.

Animals other than people cannot express their subjective feelings. However, it is possible to tell if they have the kind of representation just described. Studies of object recognition indicate that they do. For example, when given a choice between exploring a novel object and one previously experienced, a "familiar" object, rats will spend more time exploring the novel object. Rats with damage to the hippocampus will also explore a novel object more than a familiar one. However, what they apparently cannot do is remember the context in which a particular object was experienced. A normal rat that explores object 1 in Context A and object 2 in Context B, will explore the objects as if they were novel if object 1 is tested in Context B and object 2 is presented in Context A. This means the representation of the object was bound together with features of the context in which they were explored. This kind of representation should require an index and be dependent on the hippocampus. In fact, rats with damage to the hippocampus treat explored objects as familiar whether they are tested in their training context or the other context (Mumby et al., 2002; Eacott and Norman, 2004; see Eichenbaum et al., 2007 for a review).

The Hippocampus Automatically Captures Information

As noted the episodic memory system is always online, automatically capturing the events that make up our daily experiences. The studies just described also make the case that this property also depends on the hippocampus. To appreciate this point, reconsider the context-dependency of object recognition. There are no explicit demands embedded in an object recognition task. Nothing forces the animal to remember that object 1 occurred in Context 1 and object 2 occurred in Context 2, anymore than there is for the normal person to remember where he/she had breakfast. However, this happens and it depends on an intact hippocampus.

Consider another example based on a different version of the object recognition memory. In this case the rat is allowed to explore two different objects that occupy different locations in a training arena. For example, object A might be in the corner of the area and object B in the center. The normal rat stores a memory of the position of these objects because if their positions are reversed during the test, they will be explored as novel. Nothing forces the normal rat to remember the location of the objects. Rats with damage to the hippocampus, however, are not sensitive to changing the location of the objects (Mumby et al., 2002; Eacott and Norman, 2004). Thus, the hippocampus supports the processes that automatically capture information.

The Hippocampus Captures Single Episodes

There is good evidence that the hippocampus is part of the memory system that captures single episodes. For example, when the location of the hidden platform of the Morris (1984) water task is altered on a daily basis, normal rats show dramatic improvement even on the second trial, even if the intertrial interval is 2 h. In contrast, rats with damage to the hippocampus show no improvement. Moreover, an injection of the NMDA-receptor antagonist AP5 into dorsal hippocampus prior to the first trial also dramatically impairs performance on the second trial (Steele and Morris, 1999). Morris's group also has developed and used a landmark, place learning task to make the same point—that the hippocampus is part of the episodic memory system that captures information from a single experience (Day et al., 2003; Bast et al., 2005).

Pattern Completion, Cued Recall, and Conditioning to a Memory

An important implication of indexing theory is that when a subset of the features that made up an episode activate the hippocampus, the index will activate the entire pattern of neocortical activity generated by the episode. This implies that it should possible to demonstrate cued recall of a memory in animals. There is good evidence that this occurs (see Rudy and O'Reilly, 2001; Rudy et al., 2004).

A compelling example is based on the context preexposure/immediate shock paradigm. Rudy and O'Reilly (2001) used this paradigm to demonstrate that rats can actually condition to the memory of an explored context. Depending on the condition the rats were preexposed to one of two very different contexts, Context A or Context B. During the preexposure session, they were transported several times to the context. The purpose was to establish a link between the transport (T) cage and the context. Thus, for some rats T was linked to Context A (T-A) but for others it was linked to Context B (T-B). On the immediate shock day, the rats in both conditions were transported and placed into a third context, C, that had never been experienced and immediately shocked. The rats were later tested in the place they were actually shocked, Context C, or in Context A.

Note that if the indexing theory is correct, rats in neither condition should display fear to Context C, because they did not have the opportunity to construct a representation of that context before they were shocked. However, rats in the T-A condition should display fear to Context A. This is because the transport cage should activate the memory representation of Context A prior to shock and it would be available to associate with shock. In contrast, rats in the T-B conditioning should

not display fear to Context A because the representation of B not A would have been associated with shock.

This is exactly what Rudy and O'Reilly (2001) reported. Moreover, damage to dorsal hippocampus or inactivating it, prevents this result (Rudy et al., 2002; Matus-Amat et al., 2004). So, these results indicate that rodents acquire representations of context that can be activated by a subset of the features that made up the episode. In other words pattern completion can support cued recall in animals other than people and this depends on the hippocampus. It is important to appreciate that Morris and coworkers have used a totally different "paired associate" paradigm to also demonstrate cued recall that depends on the hippocampus (Day et al., 2003).

More refined studies have implicated what Marr (1971) called the autoassociative area of the hippocampus - the CA3 region, in pattern completion. Nakazawa et al. (2002) reported that a deletion of the NR1 subunit of NMDA receptor selective to the CA3 area impaired performance on a spatial pattern completion task. Gold and Kesner (2005) used ibotenic acid to selectively damage cells in the CA3 region to make this point. In their experiment rats had to learn the location of a specific food well in relationship to a distinct set of four visual cues that surrounded the test arena. Control rats could locate the food well when only one of the four visual cues was present at testing (thus, the presence of just one of the visual cues allowed pattern complete to the location of the rest of the set to guide performance.) Rats with damage to the CA3 region performed as well as control rats when tested with the entire set of cues. However, when two or three of the cues were deleted on the test trial their performance deteriorated but the control rat's performance did not.

Pattern Separation and the Hippocampus Index

One of the important properties of the episodic memory system is that it keeps similar episodes somewhat distinct. As noted, an index in the hippocampus provides an advantage over a straight neocortical memory system. There is evidence that pattern separation is better when the hippocampus is intact. One source comes from studies of generalized contextual fear conditioning. Rats with damage to the hippocampus prior to contextual fear conditioning show as much fear to the training context as intact rats. A difference emerges, however, when they are tested for generalized fear to a similar but not identical context. Rats lacking a hippocampus display more generalized fear than does the intact rat. Thus, the hippocampus provides processes that enable the rat to discriminate the context paired with shock from a similar one that was not paired with shock (Frankland et al., 1998; Antoniadis and McDonald, 2000).

Gilbert and Kesner (2006) have provided another source of evidence. They reported that rats with selective neurotoxic damage to the DG could discriminate the location of two identical objects (one of which covered a food well) when the physical distance between them, that is their spatial separation, was large but performed poorly as that distance decreased. In contrast, normal rats were unaffected by the degree of spatial separation. Thus, the hippocampus was necessary for the rats to remember separate similar spatial locations.

The Index and Systems Consolidation

The index provides a route by which the hippocampus can interact with the neocortex. In principle then it could participate in what is now called systems consolidation - a process by which the hippocampus interacts with the neocortex to strengthen connections among the neocortical activity patterns. The net effect of this type of consolidation is that connections among the neocortical ensembles are strengthened to the point that the hippocampus is no longer required for retrieval. This idea could in principle explain why old memories are believed to be more resistant to disruption than more recently established memories, also known as Ribot's (1890) law.

The concept of systems consolidation is currently controversial. There is considerable disagreement about how to interpret data based on testing of human patients with damage to the hippocampus (see Nadel and Moscovitch, 1997; Bayley et al., 2006; Moscovitch et al., 2006; Squire and Bayley, 2007). Studies with animals have established that retrograde damage to the hippocampus following either place learning or contextual fear conditioning disrupts test performance regardless of the interval separating training and surgery (Sutherland et al., 2001; Winocur et al., 2001; Clark et al., 2005a,b; Martin et al., 2005; Lehmann et al., 2007). However, there are other studies that suggest that older memories are more resistant to damage to the hippocampus than new memories (Ross and Eichenbaum, 2006). Given the current state of affairs, this aspect of indexing theory remains unsettled. However, whether this implication is true or false has no bearing on the critical beliefs that motivate the theory–*the index provides a rapid and economical way to rapidly establish episode memories, meaning that it is not necessary to strengthen connections among the cortical ensembles, and most of what is initially stored is of little importance and will be forgotten.*

CONCLUSION

The indexing theory of the hippocampus offered a set of principles that demonstrated how the intrinsic organization of the hippocampus, its anatomical relationship to other regions of the brain, and its synaptic physiology could be integrated to support how episodic memories might be acquired, stored and retrieved. In its most general form the hippocampal memory indexing theory proposed that the hippocampal index is a map not just of Euclidean space (O'Keefe and Nadel, 1978) but of cognitive space as well. It represents a transformation of the cortical space of the organism (Teyler and DiScenna, 1985, 1986). The central ideas of the theory can be found in one form or another in many contemporary accounts of how the hippocampus contributes to memory and continue to guide empirical work.

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