Theory article

A Theory on the Singular Function of the Hippocampus: Facilitating the Binding of New Circuits of Cortical Columns

Robert A. Moss *

North Mississippi Medical Center, Tupelo, MS 38801, USA

*Correspondence: Email: rmoss@emotionalrestructuring.com; Tel: 417-761-4579

Abstract: Despite the hippocampus being extensively studied, controversy remains as to its role in cognitive processing. The current paper presents a theoretical argument that the hippocampus has only one purpose: the binding of parallel cortical circuits. The paper begins with a discussion of cortical columns as the common binary digit (bit) for all neocortical processing. This is followed by details on the Dimensional Systems Model and its explanation of cortical circuitry. As opposed to any independent function in cognitive processing, the hippocampal cells are viewed as serving a slave function to cortical circuits since they are activated as part of a cortical-hippocampal-thalamic-cortical circuit. As part of that circuit, the hippocampus serves the role of reactivating the cortical circuits involved in complex memories (i.e., involving multiple cortical circuits) to facilitate the consolidation of the involved cortical columns' interconnections. Next there is a brief discussion of prior theoretical views explaining hippocampal involvement in memory and spatial representations. To facilitate an appreciation of the unique aspects of the new model, it is contrasted against the extensively developed Component Process Model. Conclusions focus on how a complete model of cortical cognitive processing is necessary to adequately explain the purpose of the hippocampus, viewed as a complex structure with an elegantly simple function.

Keywords: hippocampus; dimensional systems model; memory; cognitive functions; cortical column; neurogenesis

Abbreviations:

α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA); Dimensional Systems Model (DSM); Dynamic Causal Modeling (DCM); Gamma-amino-butyric-acid (GABA); N-methyl-D-aspartate (NMDA); Parvalbumin (PV); Pyramidal interneuron gamma (PING); Somatostatin (SOM); Vasoactive Intestinal Polypeptide (VIP)

1.   Introduction

It has been noted that the hippocampus has been one of the most extensively studied brain regions since the 1950s, primarily tied to its role in two distinct areas: episodic memory and representing space [1]. More recently, the hippocampus has been associated with other cognitive functions, including decision making, perception, imagination, and working memory [2]. As such, numerous theories have been generated to explain how the hippocampus may function in each of these cognitive areas. Although seeming improbable based on the range of functions found to involve the hippocampus, the current paper proposes there is a singular function of the hippocampus. That function is to allow the binding of parallel circuits of cortical columns.

Prior to discussing binding in relation to previous theories of hippocampal functioning, a brief review of the nature of cortical columns and the proposal that these serve as the functional unit of cortical processing will be discussed. Next, the Dimensional Systems Model (DSM) will be briefly described, followed by a discussion of cortical column circuits. This is followed by a discussion of prior hippocampal theories. The final section contrasts the current theory in relation to a different well-developed theory of hippocampal functioning.

2.   Cortical Columns

The existence of cortical columns was first described by Mountcastle [3]. Two levels of vertical organization, minicolumns and columns (i.e., macrocolumns), have been described. Calvin [4] indicates minicolumns contain between 100 and 200 neurons with a diameter of about 30 µm, while columns contain at most several hundred minicolumns with a diameter of 0.4 to 1.0 mm. Calvin further discussed the unusual pattern of superficial pyramidal neurons that support a columnar organizing principle. The collateral axon travels a characteristic lateral distance without giving off any terminal branches, but then produces a tight terminal cluster. The distance corresponds to the size of a column and may proceed for several millimeters.

The concept that all cortical processing and related memories use columns as the binary digit (i.e., bit) was made in a theoretical review article in 2006 [5]. It was suggested that the minicolumns are hardwired at birth and that columns of the primary receiving areas are the first to form based on thalamic-cortical connections. Once formed, the primary receiving columns' pyramidal axons have lateral projections and the intersection points where the terminal branches of two or more primary receiving columns meet leads to the formation of a new column. This process is proposed to occur in

similar fashion across the cortex. Columns were proposed to overlap such that they could share minicolumns with other columns. This design allows for a large number of damage resistant (i.e., due to the large size) bits. It was later suggested [6] that only boundary minicolumns synchronize to form the columnar bit, being supported by a study using a network model-based simulation of Hodgkin-Huxley neurons [7]. That study demonstrated that within both three cell and three network population circuits, there is self-organized zero lag synchrony of outer cells and populations while the inner cell and population were asynchronous.

Support for minicolumn hardwiring was provided by Perin, Berger, and Markram [8] based on whole cell recordings of layer 5 pyramidal neurons in 14- to 16-day old rat somatosensory cortical slices. The highest number of synaptic cluster connections were separated by a mean distance of 100 to 125 μm, extending beyond individual minicolumns. The cell assemblies were not arranged randomly or in lattice, but as small world networks without hubs. The authors suggested that experience could mold overall neuronal circuitry by combining elementary assemblies. They further noted this allows for vast memory storage capacity while ensuring the stability of memories in the face of ongoing activity. Based on this study, it was noted in a theoretical review [6] that minicolumns may also overlap which can further increase the number of potential minicolumn-sharing columns.

Columnar organization has been shown to exist beyond primary receiving areas [9]. In humans, fMRI has shown columns in primary auditory [10], primary visual and V3 [11], ocular dominance [12], orientation [13], and MT [14] cortices. The existence of overlapping columns has been reported in primate temporal lobe [15,16] and dorsolateral frontal cortex [17]. Jones and Rakic [18] posit that columnar-based input may lead to columnar-based output despite this not receiving much consideration in the past. Roe et al. [9] predicted that a columnar-based understanding will provide a fundamental component for the development of a connectional theory of cortical functioning, and that methods currently exist to allow *in vivo* functional tract tracing in monkeys.

In a more recent theoretical review article [19], it has been suggested that columns dynamically form. It was posited that columns are dynamically formed in a weak pyramidal interneuron gamma (PING) model fashion. In that manner the information represented by a column is quickly relayed forward requiring only a few pyramidal cells and involving α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors. However, the immediate strong inhibition from simultaneously activated interneurons limits the duration (via parvalbumin, or PV, interneurons) and spread (via somatostatin, or SOM, interneurons) of the efferent activity associated with the column. Elongated glial cells were suggested to provide longer term inhibition. Both the column integrity and its connection to other columns in the circuit involves a posited consolidation process involving vasoactive intestinal peptide (VIP) interneuron disinhibition of the boundary minicolumns and N-methyl-D-aspartate (NMDA) receptors. It was suggested that the required reactivation across the cortical circuit was accomplished by reentrant

processes and/or a cortical-hippocampal-thalamic-cortical circuit. Table 1 shows the posited neural cells in relation to dynamic column formation.

Table 1. Neuron/Receptor Function in Dynamic Cortical Column Formation. Reprinted from Moss and Moss [19] by permission of authors.

Cell/Receptor Type	Function in Column Formation and Strengthening
	Column and Columnar Circuit Formation
AMPARs	AMPARs of the PCs are associated with initial propagation of activation to downstream columns providing the activation of PCs that drives the inhibitory interneurons that lead to gamma oscillations via a PING model.
PV	PV interneurons are involved in the synchronization of the column "signal" by promoting gamma oscillations via inhibitory connections with PCs (as in PING models).
SOM	SOM interneurons influence the horizontal spread of inhibition to surrounding columns. Inhibition around a newly formed column enhances strengthening of the memory. The columnar coherence (the "signal") would be enhanced through the inhibition of overlapping and adjacent columns ("noise").
SBCs	SBC interneurons establish the column boundary via disinhibitory control of layer 5 PCs via inhibitory connections to layers 2/3 interneurons would otherwise inhibit layer 5 PCs. Leads to activation of NMDARs and strengthening of columns as detailed below.
	Column Strengthening/Consolidation
NMDARs	NMDARs of the PCs are involved in the synaptic strengthening, or memory consolidation processes. NMDAR calcium permeability means that the NMDAR-mediated currents provide longer excitability durations necessary for synaptic strengthening.
VIP	VIP interneurons control both SOM and PV cells by inhibition of other inhibitory interneurons (i.e., disinhibitory control). VIP interneurons inhibit some of the PV interneurons for a short duration and a larger percentage of the SOM interneurons for a slightly longer duration, allowing disinhibition of the longer duration NMDARs to serve as the strengthening connections of the proposed peripheral minicolumn PCs to their targets.
NGC	Elongated neurogliaform cells provide complete inhibition of all neuronal activity in the projection area of their axonal field. Via inhibition of all other interior minicolumns and minicolumns from overlapping columns, they increase the signal-to-noise ratio allowing newly formed columns to strengthen.

A recent study by Lee et al. [20] has described a similar canonical organization of Layer 1 inhibitory and disinhibitory interneuronal circuits in rat barrel cortex. In relation to mouse entorhinal cortex, Salkoff et al. [21] showed results supporting a PING model consistent with *in vivo* and *in vitro* results in the hippocampus and other cortical areas. The authors noted that pyramidal neurons typically discharge a few milliseconds before the fast-spiking interneurons.

In relation to possible dynamic formation of columns, several interesting points have been made [5,6]. First is that columns form in AND-gate fashion such that in the posterior lobes local efferent projections from two or more lower-order (i.e., representing less organized information) columns intersect and form a higher-order column. Frontal lobe columns are suggested to follow a decoding pattern proceeding from higher-order to lower-order columns, with the lowest-order columns corresponding to the behavioral output from the cortex. Since the higher-order column formation represents the information of its lower-order columns and its formation is dependent upon the location where efferents cross, a logical assumption is that if the information represented in the lower-order columns changes, the higher-order column will also change the representation of that column. This has been shown in cat visual cortex [22].

It has been a long-held belief [23] that, in adulthood, orientation columns have a segregated architecture leading to a relatively inflexible organization in the striate cortex. Bachatene et al. [22] provided results that with altered input not only can new orientation tuning occur in adapted cells of an orientation column, but also in non-adapted cells in other orientation columns. They noted this removes the possibility of an orientation hole in the new hypercolumn. They concluded that their results support columnar organization as a functionally dynamic processing unit rather than an anatomically-based structure. After a discussion of columnar circuits, the manner in which the DSM explains how non-adapted columns change orientation tuning will be presented.

A second aspect related to a column functioning as a bit means there should be rapid propagation of the information it represents, followed by immediate inhibition. Thus, from the point of sensory input to the point of output, excitatory cells should initially activate in a column followed by blanket inhibition. Based on expected consistency across circuits, this pattern is also expected in the hippocampus, but with fewer total cells being involved. If it is accurate, then it is expected that there should be cross species patterns, such that evidence of cell assemblies as opposed to individual neurons consistently involve pyramidal activation followed by blanket inhibition.

One of the better known distinctions between rodent versus primate cortical processing is related to vision [9]. There is clear evidence of primary receiving area retinotopic columns in primates, but not in mice and rats. In the discussion [19] of dynamic columns it was speculated there may be a lack of evolutionary significance for segregated primary receiving columns, but there may actually be overlapping columnar activation throughout rat/mouse visual cortex. In mouse primary visual cortex, it has been shown all starter cells are pyramidal cells [24]. Pyramidal cells in V1 have been shown to be largely stimulus-dependent [25,26] whereas interneurons had broader selectivity. Sadovsky and MacLean [27] noted feedforward wiring that was topologically efficient within a

modular network. V1 contained multiple discrete circuits that were overlapping and highly interdigitated, but were distinct from one another. In relation to natural scenes, Rikhye and Sur [28] reported that strongly correlated neuron ensembles reliably and accurately encoded visual stimuli. They concluded that coordinated activity of specific subsets of neurons underlies the reliable coding. These studies support the possibility of overlapping columns in rodent primary receiving visual cortex.

Another aspect of dynamic columns has to do with the speed with which columns are activated that provide efferents to higher-order columns. With stable input of a single sensory modality, such as sound frequency, more symmetrical columns are expected. However, if there is rapidly changing stimulus input to higher-order columns formed in dynamic fashion, such as with movement, then information based on visual and proprioceptive stimuli rapidly changes. Logically speaking, it seems that columnar formation shape will vary. Even though multiple shapes of neuronal assemblies have been described, to the current author's knowledge there are no studies that have evaluated the possibility that shape variations result based on the afferent input. However, some support for this can be taken from work with grid cells in the medial temporal cortex. There is evidence that functional micro-organization is present in grid cells similar to that described in sensorimotor regions [29]. The possibility that entorhinal cortex activity may involve columnar organization [30] has been presented.

With temporary inactivation of the rodent hippocampus, the matrix-like hexagonal grid pattern was extinguished [31] which shows the influence of input on the activation patterns. In a separate study [32], passive transport, which removed velocity modulation, was also found to disrupt grid cell firing patterns. Of note is the identification of spatially periodic cells [33] that can generally deviate from hexagonal symmetry, such as becoming more elliptical or band-like. In a recent paper [34] additional information was provided in support of the original article, noting these data are incompatible with a continuous attractor model. The proposed dynamic, overlapping column aspect of the DSM may serve to explain the findings in that nearby cells may represent different information, but still involve neuronal assemblies in the conveyance of that information.

It has been noted in the rat that the spatial organization of grid-firing is more apparent at faster rather than slower running speeds [35]. In humans [35] who explored a virtual reality environment, fMRI revealed a similar signal in a network of entorhinal/subicular, posterior and medial parietal, lateral temporal, and medial prefrontal areas. If information is conveyed within a columnar circuit, pattern matching of columns seems likely. Of note is a recent study [36] with humans that discovered a hexagonal grid-like pattern during non-spatial cognition in the entorhinal cortex and ventral medial prefrontal cortex which may indicate a common design of neuronal assemblies. Although being non-spatial in nature, the task involved subjects imagining ballistic movements of morphing birds. Thus, movement was still involved and this appears to be a common denominator in relation to the hexagonal grid-like pattern.

Although different terms (e.g., blobs, rich club, cell assemblies) have been used to describe neuron population based modules, the current paper uses the term column regardless of the shape. A major distinction of the manner the DSM describes columns is that these are not determined in an "attractor" or a "winner-take-all" fashion. Instead, they are dynamically formed based on cortical architecture from the input of lower-order columns, being discrete units. Since columns function as binary information units there is no other form of signaling, such as that based on frequency codes or wave propagations.

2.1. Overview of the Dimensional Systems Model

Strongly influenced by Luria's [37] views, the DSM [5] provided an explanation of how information processing occurs from primary through tertiary lateral cortical regions based on columnar circuits. Subcortical inputs influence memory formation by increasing the activity of those circuits. As circuits are activated and reactivated, there is an increase in glutamatergic excitatory neurotransmitter stores in the axonal boutons which increases the probability of lower-order columnar input activating the respective higher-order columns. If a circuit continues to be activated, there will be increased structural connections (i.e., axonal sprouting, increased dendritic spines) at the synaptic level. With structural connection increases, the memory represented in that circuit becomes more resistant to damage and the likelihood of forgetting decreases. In this case forgetting simply refers to the failure of downstream columns to activate upstream columns.

For example, it was discussed [5] that the reticular activating system can influence the cortical circuits via thalamic reticular nuclei. The reticular nuclei can increase thalamic activation of cortical column circuits. Similarly, increased limbic activity (e.g., amygdala) can increase cortical activity and increase the probability that columnar circuits will consolidate via increased neurotransmitter stores. The interested reader can refer to the theoretical reviews [5,6] for more detail and supporting studies. For the purposes of the current discussion, this means that microscale chemoarchitecture events represent the first step in increasing synaptic connectivity in the columnar circuit. There is recent evidence [38] that microscale chemoarchitecture of cortical areas has a direct stimulating influence on the emergence of macroscale functional connectivity patterns in the macaque. Another study [39] using human and macaque data sets suggested that cortical areas with an overall more excitatory character (based on glutamatergic AMPA and metabotropic muscarinic acetylcholine type 1 receptors) show higher levels of intrinsic functional connectivity. Of particular relevance to the later discussion of cortical circuitry will be the cortical-hippocampal-thalamic-cortical circuit involved in cortical memory consolidation [6].

There are two types of circuits proposed to exist in the neocortex: serial and parallel circuits. An example of a serial electrical circuit is a switch, battery, and light bulb interconnected with wires. If the switch is closed, the light bulb glows. If there is a separate circuit with its own switch, battery, and buzzer, there is no expectation the buzzer will sound when the light bulb circuit is activated since it is not part of that circuit. If the buzzer is connected in the same circuit as the light bulb, it is

expected it will sound at the same time the light bulb glows since it is part of that same circuit. This is a serial circuit as well. If separate light bulb and buzzer circuits share a common switch, then both will activate simultaneously with switch closure. These circuits are now working in parallel.

The DSM [5,6] makes several important points in relation to columnar circuits. First, circuits are the same throughout the cortex which means all cortical processing and memory involve the same physiological processes. This concept has been discussed by Harris and Shepherd [40] who noted the cellular organization is broadly similar both between species and cortical areas. They indicated the ensemble of circuit connections constitutes a basic circuit pattern that appears repeated across the neocortex. The DSM indicates qualitative difference in circuits is determined by the information represented by the columns in each of those circuits. If an auditory column is activated in a circuit, it will be perceived as auditory. If a visual column is activated, it is perceived as visual. If the visual and auditory columns are parts of the same circuit, being directly connected, this is a serial circuit. However, if they are not in line and are two independent circuits, but are simultaneously activated, these are parallel circuits.

A relevant example of a serial circuit is learning to do mirror drawing. The dorsal visual circuit (connected to the frontal eye field) and the hand somatosensory circuit (connected to the hand motor cortex) converge in the parietal lobe, while the related frontal eye field and motor planning circuits converge in the frontal lobe (thus being in series). However, if the individual is required to provide a verbal response indicating the recollection of having engaged in the task in previous sessions, there is an additional circuit activated at the same time, or in parallel. That circuit involves the temporal auditory cortex and the frontal operculum. It is the contention of the current paper that the hippocampus is always activated in conjunction with cortical circuits. Notably, it is only critically necessary for memory consolidation if parallel circuits are to be bound, in this example being a declarative memory. Thus, a patient (cf., HM in Milner [41]) with sufficient medial temporal lobe damage can show improvement in mirror drawing across sessions, but be unable to verbalize having done the task in the past.

This concept can serve to explain the findings of another interesting case. H. C., a 23-year-old woman with developmental amnesia and significantly reduced hippocampal volume bilaterally, was the subject in a study of face recognition [42]. In comparison to control subjects, she showed intact ability to recognize faces she encoded from a fixed viewpoint but significantly impaired ability to recognize faces from variable viewpoints. The authors indicated the results support the conclusion that compromise in the hippocampal system led to disruption in her ability to bind item features and her recognition ability that requires flexible relational representations.

The DSM agrees and explains that the recognition of the fixed viewpoint is the result of a serial circuit and memory consolidation occurred. However, the variable viewpoint involves parallel circuits based on the same face being shown in a slightly altered position that leads to a change in the bottom-up columnar circuits and different higher-order columns activating for each face orientation. The control subjects had the ability to bind the two different higher-order columns to a common

higher-order column across the five study blocks while H. C. lacked the ability to bind these parallel circuits with a common higher-order column.

Based on the DSM, all declarative memories (actually all traditionally described conscious memories since these are generally defined as one's having verbal awareness) involve the verbal interpreter [43,44] circuitry, typically in the left frontal operculum. The point will subsequently be supported that multiple parallel circuits are often activated in the absence of the verbal interpreter circuitry, thus requiring hippocampal involvement for consolidation.

2.2.   *Verbal interpreter columnar circuitry*

The concept of the left hemisphere being involved with verbal-thinking was proposed by Moss in a clinical treatment manual in 1992 [45], being updated in revised treatment manuals in 2001 [46] and 2015 [44]. Gazzaniga [47] discussed a similar concept and he called it the interpreter. Due to the accuracy of his concept the term verbal interpreter was adopted by Moss [5].

Several papers can be used in support of this concept. Wagner et al. [48] provided data that the left inferior prefrontal cortex may act as a semantic executive system that mediates retrieval of long-term conceptual knowledge, regardless of perceptual form (i.e., words and pictures). In a review of studies, Badre and Wagner [49] discussed evidence supporting that, in relation to cognitive control of memory, the left anterior and left middle ventral lateral prefrontal cortex provides controlled retrieval and post-retrieval, respectively.

The left frontal cortex has been shown to be involved in successful word recognition of both shallow and deep level of processing, as was the left hippocampus [50]. Another study [51] has provided support for the existence of a ventral frontal to temporal pathway involved with the cognitive control of episodic memory retrieval. In macaques, the ventral lateral prefrontal cortex has been shown [52] as involved in response to species-specific calls. This was suggested to be a precursor to audio-vocal integration that ultimately gave rise to human speech. Based on their recording of task-related neurons with two macaques, Bruni et al. [53] proposed that this frontal region may host an abstract "vocabulary" (author's italics) of the intended goals pursued by primates in their natural environments.

In relation to declarative or episodic memories, these are defined as the individual being capable of providing relevant verbal information. The DSM views the verbal interpreter cortical circuitry as a sequential action (two of the DSM dimensions discussed later) processor and just one of many parallel circuits that exist. Thus, there can be multiple parallel cortical circuits involved in complex memories (e.g., spatial learning) that do not include the verbal interpreter. Such non-verbal memories are not considered to be qualitatively different in the way the columnar circuits are formed and memory occurs. One other point is that the DSM indicates there is a corresponding right ventral frontal area that handles sequential action processing, but is not expected to be verbal in nature other than perhaps limited vocabulary [5,54] related to right hemisphere functions (e.g., profanity used in reaction to a negative emotional state being experienced). Right frontal action processing circuits are

expected to have the ability to control behavior when relevant ongoing task requirements are present independent of the verbal interpreter circuitry.

2.3. *A dynamic view of dynamic column circuits*

There are several important points in the DSM's explanation of various studies of cortical functioning. First, it seems logical that in the evolution of nervous system functioning, effective coding strategies should be preserved. In the peripheral nervous system, the law of specific nerve energies indicates that if a nerve is activated, regardless of the source, the information conveyed by that nerve does not change. In medical practice this is observed when a nerve root irritation at the spinal level is perceived as pain in the extremity innervated by that nerve. A central nervous system example is thalamic syndrome in which a cerebral vascular accident damages the thalamus, but the resulting pain is perceived as emanating from a lower extremity. The point of this discussion is that a binary coding strategy in the cortex would be consistent with a central nervous system maintaining its own law of specific nerve energies. Additionally, binary coding allows an exact representation of the environment which, from an evolutionary standpoint, is expected across species.

Another important aspect involves how the cortical processing changes developmentally. Once primary receiving columns form, there is an expected developmental pattern of higher-order column formation. From a developmental perspective, the columns representing the basic components of speech perception (i.e., phonemes and syllables), are in parallel and require hippocampal involvement. For example, there are many different sound frequencies associated with the various male and female voices involved in the development of one's ability to comprehend speech phonemes. Based on the relative sound frequency changes associated with a distinct phoneme, then the hippocampus is expected to become involved in facilitating the binding of all cortical columns (for the variety of voices with different sound frequencies) to the final common phoneme column. Once formed, the phoneme columns then act in serial circuits to activate word columns. Notably, based on this model any time a phoneme column activates, its associated hippocampal cells also activate since they remain in the circuit.

This means that there are many parallel cortical column circuits that develop in which the highest-order column of each parallel circuit later in life connects as one or more lower-order columns in serial circuits (e.g., phoneme columns connecting to word columns). As those parallel circuits activate there will be a corresponding number of hippocampal cells (most notably in the dentate gyrus as later explained) that activate since these were associated with the circuits when they were originally formed. In like manner, it is expected that the perception of basic shape patterns is built upon the columns associated with line orientations, curves, and angles. Lower-order columns then form higher-order columns that can feasibly represent the 36 geons discussed in the Recognition by Components theory [55]. In this case, the geon columns develop as parallel circuits which later form serial circuits.

Support for such a circuitry pattern has been described in the ventral visual stream. Several studies with macaques show patterns consistent with that described in the DSM. As early as 2004, Boynton and Hegdé [56] discussed a model in which V2 neurons may sum the response from two orientation-selective V1 simple cells. In relation to V4, it has been reported [57] that when presented with stimuli comprised of 3 bars with appearances varying from straight line segments to "C" shaped, neuron recordings are consistent with a simple orientation-tuning model. The simple pooling is based on feedforward homogeneous or heterogeneous orientation signals from early visual areas. Martin and von der Heydt [58] indicated that spike synchrony revealed the emergence of proto-objects in feedforward fashion via AMPA receptors. They suggested that only those neurons whose border-ownership preferences are consistent with a given object's representation show synchrony. They found such synchrony for both ignored and attended objects. The authors believed that feedback grouping circuits encode binding by modulating the response strength of related feature neurons. They argued their findings indicate that synchrony reflects connectivity, not any coding-by-synchrony strategy. Thus, the pattern of grouping-cell activity forms a preliminary cortical object map.

Another study [59] noted there is converging evidence that downstream areas in the primate ventral visual pathway encode progressively complex stimulus features. Based on a reanalysis of a human data set, these authors used a feedforward deep neural network which was trained to predict the object category of over a million natural images. They found population receptive fields were explicitly tuned for object categorization and there is a gradient in the complexity across the visual stream. They concluded that there is strong support for the hypothesis that object categorization is a guiding principle in functional organization. Youssofzadeh et al. [60] used a dynamic causal modeling (DCM) approach employing electroencephalograph (EEG) and fMRI data and provided support for hierarchical early visual processing dominated by feedforward processing in both the ventral and dorsal streams. More recently, Jacques et al. [61] used fMRI and electrocorticography with humans in relation to categories of faces, limbs, cars, and houses. They found that fMRI category-selective signals in the ventral temporal cortex are each associated with feedforward neural processing within 100 milliseconds. This corresponds to transmission speeds in the timeframe we [19] previously discussed from other studies in relation to purported dynamic columnar circuits' information propagation.

Hosoya and Hyvärinen [62] discussed a hierarchical sparse coding model of natural images to explain response properties in macaque V2. It was a feedforward model that took its input from a fixed V1-like model that was fed natural image patches as input. They concluded their results support sparse coding in neural representations of natural images in V2. We have discussed sparse coding to be consistent with a weak PING model of dynamic cortical column formation [19].

Another relevant aspect tied to a dynamic view of involved columnar circuits is there is a tendency to view results from neuroimaging studies as snapshots as opposed to being part of a series of events, such as in a video recording. An example is in a commentary we made [63] in relation to

how the DSM explains the results of a DCM study described by Pinotsis and Friston [64]. In this case, the point was made that despite not being discussed in the methods section monkeys were obviously first trained to make an operant response and this operant response was subsequently used to reflect when the monkey was able to discern a difference in color stimulus presentation. It was found that there was a larger area of visual cortex activated when there was a more difficult discrimination involved. As opposed to the larger area of visual cortex being activated due to bottom-up factors, the DSM indicates this is better explained based on top-down factors. The larger visual cortical area associated with difficult discriminations is the result of a larger number of lower-order visual columns being involved to determine when a different higher-order column is activated. In other words, if there is an easily perceived difference between two stimuli, the higher-order columns do not share lower-order columns and no re-activation of lower order columns is necessary to make the discrimination. This leads to a relatively faster response with less overall visual cortex metabolic activity. In the difficult discriminations, lower-order columns are shared by different higher-order columns and require each of the frontal lobe columns corresponding to the lower-order columns to reactivate their respective lower-order columns until the non-common columns can be discriminated. Once that occurs it is possible to activate two distinct higher-order columns to allow the discrimination. Thus, there is a slower response with a larger area of increased metabolic activity.

In summary of the foregoing discussion, these points indicate that interpretations of studies tied to local cortical functions necessarily require a complex, dynamic view. This includes developmental considerations because later observations of cortical activity depend on earlier circuits that were initially parallel in nature that later become serially connected with their respective higher-order columns. Additionally, there should be consideration of events and training that can lead to cortical circuitry alterations, particularly those top-down in nature, prior to interpretations of localized functions assessed in a given experiment. One final point in this discussion is that multiple circuits may be activated at the earliest stages of stimulus processing, as well as divergent circuits that later activate based on a common early stage circuit.

For example, Zeki [65] discussed there are at least three feed-forward anatomical hierarchies that reach V1 and other specialized visual areas. The author's conclusion is there are multiple, parallel, and asynchronous hierarchies in the visual brain. In a study evaluating intrinsic functional connectivity in the human brain, Yeo et al. [66] concluded that association cortex is made up of multiple, interdigitated large scale networks that possess a predominantly parallel organization. Weiner and Grill-Spector [67] proposed a model for neural representations of faces and limbs in human visual cortex that involves three processing streams extending dorsally, laterally, and ventrally. Another recent study Lafer-Sousa, Conway, and Kanwisher [68] provided evidence in the human ventral visual pathway of parallel bands of face, color, and place selectivity similar to that observed in macaques. Bracci and Op de Beck [69] noted with human subjects there was a transition from low-level pixel-based to high-level perceived shape to category along the posterior-anterior axis.

The nature of category representations differed in two pathways with ventral areas representing object animacy and dorsal areas representing object action properties. Thus, there are multiple streams in close proximity in addition to the major streams (e.g., "what" and "where" processing streams) most frequently discussed.

2.4.   Circuits of Columns

Based on the mode of processing and the information represented by columns, several DSM dimensions were described in two theoretical review articles [5,6]. These dimensions are described in Table 2 and can explain the processing mode and cortical location of columns involved with specific functions. As such, those functions requiring parallel circuits will necessarily have cortical locations to which the distributed circuits project. One dimension, the lower-order to higher-order column pattern of the posterior cortices and the higher-order to lower-order decoding pattern of the frontal lobes, has already been discussed.

The other DSM dimensions and cortical locations will be briefly discussed since these can serve to explain the location and number of hippocampal cells involved with various functions. This is based on a simple rule—one or a few excitatory hippocampal cell(s) correspond(s) to a specific columnar circuit. As such, it is best to view the activation of hippocampal excitatory cells as serving a slave function (i.e., they activate anytime their corresponding circuits activate) and the only independent purpose of a hippocampal cell is to reactivate the columns in the parallel circuits to allow consolidation. In this case the master of the hippocampal excitatory cell is the specific highest-order cortical column that represents all lower-order columns that define that specific circuit.

Global processing of the right hemisphere involves fewer columns in a circuit from the point of reception to the planned behavioral output. The left cortex involves more columns from reception to action, being termed Analytical. Moss et al. [6] cited studies in support of this distinction. For example, in relation temporal lobe Brodmann's area 22, a post-mortem histological study [70] found neuronal tract tracing reveals a modular pattern of connections linking regularly spaced clusters of neurons. The authors believed the clusters were consistent with interdigitating subsystems of interconnected columns with wider spacing in the left hemisphere. Calculations suggested that the left hemisphere cortex can contain about 30% more distinct subsystems within the same volume of tissue. In a review [71] on asymmetries there was reported support for a greater number of interconnected columns in the left cerebral cortex. Using diffusion-weighted MRI with humans and nonhuman primates, Iturria-Medina et al. [72] found results supporting the left hemisphere has a leading role for highly demanding specific processes requiring dedicated specialized networks, whereas the right has a leading role for more general processes requiring a relatively greater general level of interconnectivity. In relation to the hippocampus, large variations in the number of hippocampal cells are not expected from right to left because the hippocampal cells correspond to the circuits, not the number of individual columns within the circuit.

Table 2. Dimensions of Cortical Column Organization in the Dimensional Systems Model. Reprinted from Moss and Moss [19] by permission of authors.

Dimension Name	Description of Dimension
Internal-External	The medial cortical columns code stimulus information that is internal and self-referential while the lateral cortex codes for external stimuli. Intermediate or transitional zones code for combinations of both.
Proximal-distal	In relation to proximal versus distal to the body stimulus coding, the central sulcus is considered the most proximal cortical location. The post-central sulcus parietal cortical area would code for somatosensory (i.e., body sensation) stimuli. Both vision (occipital lobe) and audition (temporal lobe) involve distal sensory information. The pre-central sulcus primary motor strip involves the body directly while anterior prefrontal processing involves information manipulation largely independent of the body.
Simultaneous-sequential	Ventral cortex processes in a sequential manner and dorsal cortex in a simultaneous manner, with intermediate areas using both modes of processing.
Reception-action	The parietal, temporal, and occipital lobes contain all receptive, or sensory, information while the frontal lobes code for all action-related information.
Unorganized-organized	Receptive information progresses from less-organized, or lower-order, information to more-organized, or higher-order, information (i.e., coding) as the stream moves away from the primary sensory receiving areas (i.e., bottom-up processing). On the other hand, the frontal action columns progress in a rostral to caudal more-organized, or higher-order information to less-organized, or lower order information (i.e., decoding) as the stream goes toward the premotor and primary motor areas. The frontal action columns' control of posterior lobe receptive columns is also present (i.e., top-down processing).
Analytical-Global	Each cortical hemisphere acts as a separate, albeit interconnected, processing unit which means that each of the aforementioned dimensions is contained within each hemisphere. However, there are fewer columns from the time of sensory input to the response level in the right hemisphere. This means that the right cortex can process information faster, but with fewer details (i.e., global processing). The greater number of interconnected columns in the left hemisphere allows more detailed processing and memory storage (i.e., analytical processing)

The next dimension involves internal versus external coding. Lateral cortex codes for external self and environmental stimuli whereas medial cortex codes for self-referential and internal stimuli. In keeping with what was called the default mode network [73], external-stimulus independent

thought is associated with medial prefrontal, posterior cingulate-precuneus, and posterior temporal-parietal cortex. Vantansever et al. [74] noted recent evidence suggests this network actually involves self-referential and memory-based processing. Those authors provided evidence that the same network is also involved with working memory via its interactions with other networks. In another neuroimaging study [75], medial, orbital, and inferior lateral frontal cortices were consistently activated for a variety of emotions. Moss et al. [6] theorized that cortical columns closer in proximity to the diencephalon and limbic structures code for self-referential information with a gradual transition to external stimuli as the cortex proceeds further away from the midline subcortical structures. With this in mind in relation to serial circuits, the cortical regions where the medial and lateral cortex converge (e.g., frontal pole, insula, supplementary motor) code for internal processing in relation to external stimuli. Hippocampal involvement is not required for memory consolidation of the convergent serial processing, but would become necessary if parallel internal/external convergent zone distal circuits are involved (e.g., supplementary motor activation reflecting a decision to perform an operant response of pressing a switch when presented with a light to avoid the painful stimulus which is reflected by insular activation).

Proximal coding of self to the external world involves the primary sensory receiving areas and primary motor cortex, whereas the cortical regions farthest away code for distal, or non-body, processes. Badre and D'Esposito [76] provided data supporting the rostral regions of the frontal cortex as being involved with abstract representations and more complex rules. Based on four mini-experiments that varied competition at different levels of representation, these same authors [77] concluded that there is strong support for frontal cognitive control being organized in a rostro-caudal representational hierarchy. Similarly, human medial frontal cortex shows an organizational pattern [78] such that the posterior frontal zone is associated with motor function, the middle zone is involved with cognitive control, pain, and affect, and the anterior zone is involved with reward, social processing, and episodic memory. Memory consolidation of tactile, visual, and auditory multisensory processing at the convergence zone around the temporal parietal junction would not require the hippocampus because the circuits are in series. The posterior parietal coding of a specific distal spatial location and the anterior temporal lobe coding of the specific object consistently seen in that specific location involves parallel columnar circuits and does require hippocampal involvement.

Simultaneous processing dorsally involves the coding of multiple stimuli at the same time. This contrasts to ventral sequential processing that involves processing one specific stimulus at a time, but in a set order. The logical evolutionary reason for this is that somatosensory input may involve multiple areas being simultaneously stimulated which led to the posterior parietal regions using the same mode. Similarly, auditory processing is sequential in nature and the connected ventral areas would follow the same type of processing. Along these lines vision may use both forms of processing and is located between the somatosensory and auditory areas. Where simultaneous and sequential processing merge is the location of coding for tasks requiring both, such as tracking an object and motion detection. In their review Badre & D'Esposito's [76] noted there is support for a distinction

between dorsal and ventral frontal rostro-caudal gradients, as well as the parietal and lateral temporal cortices, such that each acts as a functional network. The existence of parallel dorsal and ventral streams along the rostro-caudal axis has been shown with resting state connectivity data [79]. Based on the DSM, memory for looking at the quadrant in which a specific object in a specific location consistently appears (simultaneous processing) would not require hippocampal involvement for consolidation because it is a serial circuit. However, remembering that when one sees the picture of a car (temporal) in the left upper quadrant (parietal) means one can press a button (lateral frontal) to receive a reward (medial frontal) would require the hippocampus since parallel circuits are involved.

The final dimension involves the posterior lobes being involved with reception and the frontal lobes with action. Within the DSM it is [19,43] theorized that with the formation of a new receptive column a corresponding action column automatically forms. This is a serial circuit and does not require hippocampal involvement. The aforementioned description of the serial circuitry in performing mirror drawing is an example.

Based on the described dimensions in which distributed circuits form, from an evolutionary standpoint it is logical that bundles of axons would form to connect the cortical areas most frequently associated with that distributed processing. If only two distributed parallel circuits are involved, it is expected that there would be direct connections that develop between those areas such that the common column to which the parallel circuits project would be close in proximity to whichever circuit requires the longest processing time. For example, sequential processing would typically require a longer time than simultaneous processing, and for only two parallel circuits involving each mode, then the common column would be expected in the temporal lobe because efferent flow from the parietal area occurs more quickly. However, if more than 2 parallel circuits are involved, a more efficient manner is to have each of the involved circuits project to a common distal cortical location. An example is retrosplenial cortex that has been implicated in both rats and humans in integrating information to allow allocentric functioning [80]. Retrosplenial cortex has been described as intermediate cortex between neocortical and archicortical areas [81]. Another example would be the rostral parahippocampal cortex connected to the posterior-medial system and perirhinal cortex connected to the anterior-temporal system cortices where external (lateral) cortical information can be combined with internal (medial) information, with possible integration in the caudal parahippocampal cortex [82]. Both the perirhinal and parahippocampal cortices project to the entorhinal cortex which may combine the information prior to projection to the hippocampus. This is consistent with Paller's [83] concept of coherence ensembles (discussed in the hippocampus theories section).

Building upon the aspects just discussed, it is possible to describe how detailed episodic memories are retrieved based on the DSM. With each receptive column an action column forms. Thus, each of the columns in a circuit has its own action column. Each parallel receptive circuit has its highest-order column that represents the information in that circuit. The convergence location of the efferent projections of those parallel circuits' highest-order columns leads to the formation of a

new higher-order column. That column now represents all the information contained in the lower-order circuits (i.e., the gist) although detailed recall requires reactivation of the lower-order circuits. Eventually, a column forms (e.g., entorhinal cortex) representing all receptive information contained in the various parallel circuits. A corresponding frontal action column automatically forms to correspond to the posterior highest-order column (for all involved circuits). That highest-order action column can then activate each lower-order action column in the circuit which in turn can each activate the lower-order receptive columns in its respective circuit. That top-down processing corresponds to the detailed recollection of the various aspects of the episodic memory.

The previously discussed finding by Bachatene [22] that orientation columns change based on new input to an adjoining orientation column is best explained by such top-down mechanisms. The numerous higher-order sensory columns upstream to the new orientation columns have been formed based on additional input from columns of lower-order parallel circuits (e.g., angle columns, curve columns, geon or proto-object columns). Each of those receptive columns has its corresponding frontal action column. Each frontal action column has the capability of reactivating its lower-order columns that in turn can reactivate its associated lower-order sensory columns. Because the higher-order receptive and associated action columns are based on specific relative input (e.g., an angle column based on its respective line orientation columns), then resetting of the adjoining line orientation columns can logically occur based on higher-order action columns input to its respective lower-order columns. Obviously, whether this can actually occur has to await a modeling study based on these representations and related dynamics.

In relation to episodic memory, there is emerging evidence that retrieval involves the same areas of initial cortical processing. In humans, both EEG and transcranial magnetic stimulation supported successful retrieval functionally relies on rapid (100 to 200 ms) reactivation of visual cortex [84]. The authors acknowledged that their results cannot clarify the hippocampal-neocortical interactions involved in such early sensory cortical reactivation. In a different study [85] with humans with a visual shape orientation discrimination task, fMRI of both spontaneous brain activity and resting state showed involvement of the same cortical regions (medial/lateral parietal regions and visual cortex) recruited by the task. In rats, the medial prefrontal cortex has been shown to contribute to recall of recently acquired spatial memory [86].

These results provide support for the feasibility of the DSM position that the same cortical circuits involved in the original processing are the same ones involved with memory and that frontal columns can reactivate those columns without hippocampal involvement. A clinical example we previously discussed [63] is in relation to earlier versus late stage Alzheimer's disease patients. Based on the DSM it is expected that in earlier stages in which damage has occurred primarily in the hippocampus, accurate immediate recall of episodic information is expected because column formation occurs in the intact entorhinal cortex and its associated frontal column. In later stages at which point entorhinal cortex is impacted, there is expected to be a loss of ability to provide

immediate detailed recall due to the highest-order column associated with the lower-order circuits not forming.

2.5.   *Cortical to hippocampus connections and neurogenesis*

The medial temporal lobe afferent connections to the hippocampus have been noted as primarily from the entorhinal cortex [87] which serves as the intermediary structure between the hippocampus and many neocortical regions. Morrissey and Takehara-Nishiuchi [87] note that projections to the entorhinal cortex originate from neocortical regions directly and through the perirhinal and postrhinal (parahippocampal in primates) cortices. The entorhinal cortex divides into medial and lateral sub-regions. Projections from layer II form the performant pathway and target the dentate gyrus and CA3 of the hippocampus. Layer III projections along the temporoammonic pathway and tend to target CA1 and the subiculum. The medial entorhinal cortex projections target the middle-third of the molecular layer of the dentate gyrus with the lateral entorhinal cortex targeting the outer-third. Medial entorhinal cortical layer 3 projections target the proximal area and lateral projections target the distal part of the transverse axis of CA1. These authors indicate there are 6 different sub-fields of the entorhinal cortex which largely overlap with the dentate gyrus projections and then provide a review of the different aspects of memory impacted by the entorhinal cortex based on these sub-fields. In their conclusions they note the high level of multimodal sensory integration that occurs in the entorhinal cortex and that by studying the computations in each sub-field, it may be possible to separate the integration occurring there versus within the downstream hippocampus.

The circuit typically described [88] within the hippocampus is that dentate gyrus provides input to CA3 which projects to CA1. CA2 has been viewed as a transition zone between CA3 and CA1, although more recent data suggest it is only weakly activated by CA3 inputs [88] and that CA2 provides parallel input from the entorhinal cortex to CA1. Based on their data, Mankin et al. [88] found that CA2 only weakly codes for space and differences in context, and they believe this is consistent with social, emotional, and temporal rather than spatial aspects of memory. The DSM view of different information being represented in the hippocampal sub-regions is that each region's information depends on the associated neocortical circuits with which it is connected.

The foregoing information is consistent with the feasibility of the DSM proposal that the highest level of integration of parallel cortical circuits occurs at the entorhinal cortex level and that the connections to the hippocampus serve the role of activating associated hippocampal cells for the purpose of consolidating the related cortical circuits. If correct, there should be evidence developmentally that cortical input to the hippocampus allowing complex or episodic memories should not occur until the various cortical circuits in different regions have time to develop. A similar concept was discussed in the original DSM article in that, based on sensory input, each of the areas around the primary receiving areas of each hemisphere need to have time to form its own circuits prior to cross-communication with other cortical areas that process different information in different ways (i.e., the cortical dimensions).

Lavenex and Lavenex [89] discussed their developmental model of hippocampal areas to provide explanations of findings in episodic memory studies. They use information from postnatal hippocampal formation development from the monkey as the basis of explaining findings with human children. Prior to the age of 2, children are unable to form episodic memories for later life recall (infantile amnesia). These authors note that CA1 receives entorhinal projections early and shows early maturation. It is also observed that CA2 that is highly interconnected with subcortical structures matures even earlier. Based on their studies in humans, it is around the age of 2 when CA1 maturation occurs that basic allocentric representations of the environment occur. From the ages of 2 to 3.5 children show the ability to distinguish and remember closely related spatial locations while still showing continued deficits in long-term episodic memory (childhood amnesia). Those authors suggest subsequent improvements in spatial and episodic memory are associated with the maturation of CA3 and the dentate gyrus.

Lavenex and Lavenex [89] note that the dentate gyrus is not mature at birth, being only one of two regions in the mammalian brain that clearly shows neurogenesis. In their studies of the monkey, they found 40% of the total number of granule cells seen in adults are added postnatally. In relation to CA3 they noted its maturation parallels that of the dentate gyrus since it is downstream. Although the diagram of their model shows the entorhinal input occurs early to CA1 and CA2, with increased input to the dentate gyrus developing around the age of 3 and heavy input after the age of 7, they fail to consider the possibility that it is the cortical circuitry that gradually develops prior to the strong dentate gyrus connections.

Vivar et al. [90] used retroviral labeling to study new granule cells in mouse dentate gyrus. The results showed that newborn granule cells receive afferents from intra-hippocampal cells (i.e., interneurons, mossy cells, area CA3, and, transiently, from mature granule cells). Input from the perirhinal and lateral entorhinal cortices is sparse after 21 days and gradually increases over time. The authors noted there has been controversy as to whether there is direct innervation from perirhinal cortex to dentate gyrus, but their results show those connections are present and suggest it is possible that it occurs selectively for newborn, as opposed to mature, granule cells. Interestingly, they noted that loss of input from perirhinal and lateral entorhinal cortex does not change the number of new granule cells, but it disrupts the ability to make fine spatial distinctions. Given that the hippocampus remains intact, this observation suggests it is cortical and not hippocampal circuitry responsible for fine spatial distinctions.

Another study [91] provided similar results with those authors noting adult-born new granule cells are robustly connected to local dentate gyrus cells prior to their connection to the cortex. Drew et al. [92] reviewed the literature and concluded that there is strong evidence that neurogenesis contributes to a wide range of cognitive and emotional hippocampal functions. Neurogenesis continues in the human brain through old age which Drew et al. [92] take as an indication of its functional role.

Based on the DSM, the highest-order cortical columns of the entorhinal (and perirhinal based on Vivar et al. [90]) cortex form in response to new parallel lower-order circuits' columns input. If accurate, the need for new granule cells is based on the new highest-order column's recruitment of a new granule cell that can then initiate the consolidation process of the new episodic memory. Based on the DSM this serves to explain why cortical input does not occur until after a given new granule cell has its firm connections internally to the hippocampus. Once the new granule cell is fully integrated into the hippocampal circuitry, it is capable of initiating the consolidation processing of the hippocampus. The cortical input from the new highest-order column (that represents all lower-order columnar circuits) to the newly recruited granule cell determines which parallel cortical circuits become jointly bound. Additionally, Drew et al. [92] note that mature granule cells do not interconnect. This appears to fit well with what is expected if the only role of a new granule cell is to consolidate its associated new multi-circuit cortical memory as opposed to performing additional processing. Without new granule cells, only new serial cortical circuits would be expected to consolidate in the cortex. This is based on the assumption that existing dentate granule cells remain in line with the cortical circuits they previously served to consolidate. Since there are no dentate cells available to receive new input, there is no means for the hippocampal circuitry to systematically reactivate the parallel cortical circuits and consolidate new episodic memories.

2.6.   *The cortical-hippocampal-thalamic-cortical circuit*

Each circuit's highest order column is expected to have one or a few corresponding hippocampal cell(s), as does each of the higher-order columns representing the combined information of the involved circuits. The hippocampal cells serve the purpose of reactivating the columnar circuits and via the process of disinhibition [19] of each of the boundary minicolumns of all connected columns, the consolidation process progresses. Initially, increases in neurotransmitter stores increase the ability of interconnected columns to activate with appropriate input, followed by structural growth at the synaptic level [5,6]. Since the hippocampal neurons remain in line with the circuit, anytime the circuit activates the associated hippocampal cell activates. Based on the DSM, if the cell is monitored, its activation when a memory is recalled has been misinterpreted as its retrieving a memory or being part of a spatial map. Similarly, if the cell is stimulated, it will reactivate its associated cortical circuit and could be misinterpreted as being associated with the actual storage of that memory.

In the original DSM article [5] it was proposed that thalamic association nuclei interconnect with association cortex to allow columnar circuit consolidation. Reentrant processes between directly connected columns (e.g., posterior column and its associated frontal column) were later discussed as a contributing mechanism for consolidation [19]. The involvement of the hippocampus was discussed in a pacemaker role in the update on the DSM [6]. There are numerous anatomical connections from the hippocampus to thalamic nuclei [93]. An article that supports the cortex, hippocampus, and thalamus circuit was provided by Sperling et al. [94]. Using fMRI during the

encoding of face-name associations, a consistent pattern of activation was observed in the hippocampus, pulvinar, fusiform cortex, and dorsolateral prefrontal cortex. The authors concluded the data support a distributed network of brain regions in associative learning. Another study shows the anterior thalamic nuclei have widespread cortical and hippocampal connections [95] and are involved in memory and spatial navigation functions.

A major role has been attributed to VIP interneurons in the DSM's explanation of cortical circuit memory consolidation. Moss & Moss [19] suggested VIP interneurons disinhibit the boundary minicolumns to allow consolidation (i.e., recurrent circuit activation leading to increased glutamate stores). Referred to as a blanket of inhibition [96], many interneurons innervate nearby pyramidal cells densely and without apparent specificity. In a study with mouse visual cortex, Karnini et al. [97] noted that VIP interneurons opened holes in that blanket of inhibition with an effective range of about 120μm. This is similar to the separation of synaptic cluster connections described in the previously discussed Perin et al. [8] study. In their evaluation of barrel cortex, Wall et al. [98] found that cortical and thalamic inputs were greatest onto VIP compared to other interneuron classes.

Traveling theta waves have recently been demonstrated in human hippocampus, paralleling that in rodents [99]. Gamma oscillations often co-occur with theta oscillations to which they are phase-amplitude coupled [100]. Within mouse CA1, theta-nested intrinsic gamma was found to occur from optogenetic theta frequency stimulation in PING fashion and conducts the signal downstream [101]. These findings appear consistent with the DSM's position that the hippocampus initiates and maintains the reactivation of cortical column circuits, as well as hippocampal processing occurring in PING fashion.

A model involving replay of activity sequences reflecting previous behavior in the hippocampus [102] that involves sharp-wave/ripples has been proposed to explain hippocampal circuit learning during sleep and rest. In a separate computational model of the thalamic-cortical system [103], it was shown that input mimicking hippocampal ripples led to synaptic changes promoting replay of specific firing sequences of cortical neurons. Thus, it was suggested that sharp-wave ripple events, cortical slow oscillations, and synaptic plasticity lead to memory consolidation via replay at the cortical level. The importance of the cortical involvement during slow wave sleep independent of the hippocampus was provided by Miyamoto et al. [104]. When mice learned novel textures and consolidated them during sleep, optogenetic inhibition of top-down projecting axons from M2 to S1 impaired sleep-dependent reactivation of S1 neurons and memory consolidation. Closed-loop asynchronous M2 and S1 co-activation reduced memory retention, while synchronous closed-loop co-activation prolonged retention. The authors concluded top-down cortical information flow in slow wave sleep is required for perceptual memory consolidation. The point being drawn from these studies is that the DSM proposed cortical-hippocampal-thalamic-cortical circuit is a reasonable explanation in which the initial cortical column circuit is strengthened via reactivation of that circuit.

An additional consolidation role is described by Shimamura [105] in that the hippocampal cells associated with established memories can be more efficiently associated with new memories. If the prior studies showing dentate gyrus granule cells do not interconnect are considered, the hypothesized hippocampal process facilitating association with prior memories must occur in other sub-regions. Based on the DSM, when the older, previously consolidated columnar circuits are activated, the associated hippocampal cells are simultaneously activated in association with the new circuit's hippocampal cell. With long term potentiation occurring with hippocampal cells and the reactivation of all involved cells, synapses can quickly be strengthened among all involved hippocampal cells. This, in turn, can logically result in efficient consolidation of the new cortical circuit's common column (i.e., representing the old and new cortical column circuits).

There are a number of theories that have discussed the role of the hippocampus in relation to the concept of binding. These will now be discussed and the differences with the DSM view will be briefly elaborated.

3.   Theories on Binding in Episodic Memory

Marr [106] was the first to propose that the hippocampus is a temporary memory storage site for neocortical activity. He described the neural architecture that could allow what has been called autoassociation. In relation to episodic memory specifically, the binding role of the hippocampal complex in cortical activation associated with new experiences is part of what has been termed the Standard Model [107]. Developed by Squire [108, 109], this system-level consolidation model indicates the hippocampus acts to bind cortical representations activated at a given time via converging inputs into the medial temporal cortex. The binding of cortical representations via the medial temporal lobe increases the chances of subsequent reactivation leading to the establishment of cortical-cortical interconnections. In this view the hippocampus is part of the retrieval network for recent memories, but memories are gradually transferred to the cortical circuits for long-term storage and are no longer dependent on the hippocampus for retrieval. The DSM differs from the standard model in that frontal columns are involved in retrieval and there is no transfer of information back to the cortex because the cortical circuits already exist.

In their Multiple-Trace Theory Nadel & Moscovitch [107] accepted the cortical representations binding role of the hippocampus, but proposed that with repeated activation the cortical representations produced different, but related, traces in the medial temporal cortex. That results in more widespread links within the hippocampal complex and the multiple traces increase the probability of successful memory retrieval. A major distinction made by this model is that the hippocampus is involved in retrieval of remote as well as recent episodic memories. The DSM differs in that specific hippocampal cells correspond to specific cortical circuits and not multiple traces. Instead, the same hippocampal cells involved with encoding are the same ones that activate whenever the cortical circuit reactivates, provided there is accurate recall. In support of this DSM

view, a recent study Nakamura and Sauvage [110] provided evidence that in the rat dorsal hippocampus the same cells are involved in both activation (encoding) and reactivation (retrieval).

Competitive Trace Theory [111] holds that it is at initial encoding that memories are most episodic and veridical. With each reactivation the central features of the memory trace are present, but accurate details can be lost and replaced resulting in a slightly altered version. However, with each reactivation the new memory undergoes the same storage process as the original one. This means the new memory is not stored in parallel, it actually competes for cortical representation. Thus, the hippocampus is not the site of trace storage, but it binds the specific components of the cortical memory together. This allows the hippocampus or neocortex to retrieve the cortical memory. Finally, with increasing reactivations, the cortical traces become devoid of context, losing associated details.

In relation to Competitive Trace Theory, the DSM is in agreement with memories being more episodic at initial encoding. With reactivation of an episodic memory, the lower-order columns reactivate in each associated circuit. The least consolidated (i.e., relying strictly on neurotransmitter stores) aspect is the highest-order column of each circuit. Thus, reactivation of the lower-order columns can feasibly lead to the erroneous activation of a previously consolidated higher-order column that utilizes many of the same lower-order columns. The result is that aspect of the episodic memory can be altered, and with reactivation from the hippocampal circuitry, become consolidated in the manner described in Competitive Trace Theory. In like manner, if when recalling the episodic memory and certain aspects (and their associated columnar circuits) are not included in that recall, over time the unrecalled circuits can weaken (due to failure to develop synaptic structural connections and neurotransmitter stores lessen) in its connections. This results in the failure of lower-order columns to activate higher-order columns. In that case there is forgetting of the details associated with each lost circuit of the original memory.

Shimamura [105] offered an alternative to Multiple Trace Theory. Relational Binding Theory accepted the standard model, but suggested the medial temporal lobe contributes to or aids in accessing and retrieving remote memories by way of relational binding of cortical-hippocampal connections. This views the hippocampus as the top of the hierarchy of the relational binding. As previously discussed, an important addition made by this theory is the aspect indicating that newly formed cortical events can be integrated into pre-existing memories (e.g., schematization). The obvious difference in the view of the DSM is that entorhinal cortex is the location of the top of the hierarchy in relational binding.

A different view on the primary function of the hippocampus is Scene Construction Theory [106]. It suggests the hippocampus allows details to be connected within the coherent spatial context of a scene. Once the scenes are generated, details can be integrated and used for episodic memory, imaging future and novel situations, and spatial navigation. Also from a relational processing view, the Constructive Episodic Simulation hypothesis [107] holds that the hippocampus supports autobiographical memory in a flexible manner in which it binds together multiple episodic details. As such, new event simulations may be built by recombining the details from several past events. It

purports to explain how the hippocampus supports tasks such as problem solving and creativity. In an investigation of Scene Construction Theory, a recent study [108] provided data supporting the primary role of the hippocampus as being involved only in memory and not in spatial cognition. The DSM agrees with the memory role, but differs in its view that each of the functions being attributed to hippocampal cells, including those spatial in nature, actually occur at the cortical level.

Sheldon and Levine [109] have recently provided an integration and elaboration on the mental construction theory of hippocampal functioning. They suggest that task demands and related computations determine where activity will occur along the hippocampus. They consider pattern completion (i.e., using a portion of an existing representation to reactivate stored details) and pattern separation mechanisms (i.e., encoding events as unique codes). They propose the anterior hippocampus is engaged when a construction must converge onto a conceptual representation (e.g., open-ended retrieval demands that require establishing a goal or concept), whereas the posterior region is engaged when a construction must configure or converge on a perceptual representation (e.g., mental construction is triggered and then created around externally derived perceptual details). In that regard, their view is that the hippocampus is not a unitary structure. It is suggested the hippocampus may serve as a zone of convergence for coordinating details into cohesive constructions. They posit the hippocampus is not necessary when an already existing knowledge framework can be used to generate a representation (consistent with Paller's, [83] episodic memory view discussed next). However, the hippocampus is involved in mental task mediation when the task is open-ended, or ambiguous, or when specific perceptual details must be added. A recent paper [116] utilizing high-resolution fMRI and multivariate pattern analysis provided support for the proposition that the dentate gyrus is involved with pattern separation. Those authors provided evidence that the dentate gyrus sub-region provides representations of similar scenes that are less overlapping than the medial temporal lobe and other hippocampal sub-regions.

In relation to the proposals by Sheldon and Levine [115], the DSM view disagrees with their theory's attribution of functions performed by the hippocampus functions with the exception of consolidation. In relation to pattern separation and pattern completion, there are studies that show cortical involvement in both aspects. Pidgeon and Morcom [117] used fMRI and found neural activity consistent with pattern separation in occipital-temporal and bilateral lateral prefrontal cortex. Neural activity consistent with pattern completion was found in left anterior and right precuneus. The authors noted these results are consistent with findings of pattern separation and completion in rodent sensory cortex. In the Representational-Hierarchical Theory [118] of cortical organization related to visual cognition, there is no modular aspect. Instead, it is proposed that in the ventral flow in an occipital to temporal direction there is a hierarchical progression from lower-level feature representations to feature conjunctions to whole-object representations. In that regard, the feature conjunctions are not restricted to a single object representation, but may be involved in any object representation in which it is a component. This view is in agreement with the previously discussed studies supporting parallel hierarchical circuitry in the ventral visual pathway.

The DSM explains the findings of Beron et al. [116] of less overlap in dentate gyrus versus entorhinal cortex in that the highest-order column in the entorhinal cortex represents all lower-order columnar circuits that project to it. As a result, the lower-order columnar circuits have their own dentate gyrus granule cells that were previously formed. This was previously discussed in relation to developmental aspects in which lower-order circuits with their highest-order columns were previously consolidated. However, the DSM indicates that pattern separation is actually a misleading term since the dentate gyrus cells are simply reflections of the coding process in posterior cortical regions (i.e., lower-order input leading to higher-order representations). Similarly, pattern completion reflects the highest-order columns of the various circuits in posterior cortex.

In reference to episodic memories Paller [83] suggested these require cross-cortical consolidation which involves cortical-hippocampal and cortical-thalamic networks. He noted that, despite an inability to explain how coding of neural information occurs, distinct zones of the cerebral cortex are specialized for distinct functions and episodic memories involve these distributed zones. He suggested that coherence ensembles form in the cortex that allow newly formed episodic memories to take on meaning within the context of previously stored information. He further noted the locations may vary, but gave examples that included entorhinal cortex, temporal pole, orbitofrontal cortex, retrosplenial cortex, and posterior cingulate. When activated, the coherence ensembles allow the gist of the memory to be retrieved and their connections, in turn, enable the specifics of that cortical memory to be retrieved. Once the cortical coherence ensembles are consolidated, the hippocampus is no longer required for the complex memory retrieval. Obviously, the DSM is in agreement with cortical locations to which parallel circuits project, but disagrees with the hippocampal retrieval aspect since frontal columns perform this aspect.

Complementary Learning Systems Theory [119] indicated that the brain has two specialized learning and memory systems. The hippocampus is viewed as a sparse, pattern separated system to allow rapid learning of episodic memories; the neocortex is viewed as a distributed system involved in gradually integrating across episodes to allow the extraction of latent semantic structure [120]. This approach holds that the hippocampus can replay individual memories back to the cortex achieving an interleaving of learning experiences that is capable of eliminating catastrophic interference [120]. Catastrophic interference refers to the belief that subsequent learning tends to completely overwrite earlier learning. By replaying the memories, the hippocampus provides a way the slower learning cortex can integrate the new memories without overwriting the older ones. The nightly replay of memories learned during the day is a means of teaching the neocortex. In a more recent theoretical review, McClelland [121] explained how the theory explains rapid neocortical learning of information consistent with prior knowledge (i.e., schema-consistent) as opposed to inconsistent information that does not allow rapid learning.

Complementary Learning Theory sees the hippocampus as encoding information in a qualitatively different way than the neocortex [120]. The hippocampus necessarily keeps representations highly separated from each other leading to different neurons encoding memories,

even those of similar events or places. This is possible via the sparse levels of activation in the hippocampus. It incorporates information on pattern separation (dentate gyrus, CA3) and pattern completion (CA1) within the context of long-term potentiation and long-term depression [120].

The DSM view is that the hippocampus reactivates parallel cortical circuits for consolidation, but never has an independent function of forming its own memory representations. Additionally, there is no replaying the memory back to the cortex, only the reactivation of the cortical circuits involved in the original processing of the various aspects of the episodic memory. The hypothesized manner in which sleep leads to strengthening the synaptic connections of columnar circuits based on the DSM was previously discussed in opposition to this being associated with the hippocampus teaching the cortex. DSM views on pattern separation and pattern completion cortical processing were discussed and are at odds with Complementary Learning Theory view that this is an independent function of the hippocampus.

Eichenbaum et al. [122] discussed the research that supports the idea that different components of the medial temporal lobe make distinct contributions to the memory capacities of non-human animals that parallel features of human episodic memory. The hippocampus is specifically involved in the recollection component of item recognition, associative recognition, and spatial detail memory. These aspects allow stimuli to be represented in context. In this regard, the hippocampal neurons encode configurations of items and events in temporal and spatial context in which they were experienced. This theoretical formulation explains the role of perirhinal and lateral entorhinal cortex neurons as encoding representations of individual stimuli (object recognition) in reference to familiarity. In contrast, the parahippocampal and medial entorhinal cortex neurons represent spatial contextual features of distinct experiences. The medial entorhinal cortex is also viewed as capable of providing non-spatial context that contributes to memory recollection. Based on the parallel "what" and "where" processing streams' input from the perirhinal, parahippocampal, and entorhinal cortices, the hippocampus is viewed as supporting a "memory space" (author's quotation marks) that binds events within their context, linking related memories. In contrast to the proposals of the next section on spatial theories, Eichenbaum views place cells [123] as representing the series of places in sequence, being "episodic" (author's quotation marks) memories. Eichenbaum [124] also discussed the possible existence of what has been called "time cells" in CA1, and possibly CA2. These are viewed as representing the flow of time in episodic memories adding to the spatial information of place cells. However, Eichenbaum acknowledged that the question of whether this aspect is internally generated within the hippocampus or is based on its inputs, or a combination of both, has not been determined.

In relation to Eichenbaum's views, the DSM disagrees that the hippocampus provides a memory space for binding events. Instead, the hippocampus simply serves to reactivate the previously activated columnar circuits associated with the various aspects of the episodic memory. Thus, the lower-order columns activate higher-order ones in the various circuits, followed by the highest-order columns of those circuits activating common columns to the point that the single highest-order

column of the particular episodic memory projects to the hippocampus. Therefore, it is the sequence of circuit activations that determines which aspects become part of the episodic memory, not the fact that they coincide in time or are linked in a space without prior cortical connections. The concept of time cells is also seen as any hippocampal cell connected to related columnar circuit activations. The DSM dimension of sequential processing is a necessary component of any time-based memory and complex memories involving time perceptions are expected to occur in the context of formation of higher-order columns in the perirhinal, parahippocampal, and entorhinal cortices prior to connections to the hippocampus. A study supporting the DSM view of a cortical location of time processing was done by Eradath et al. [126]. They provided data from monkeys that perirhinal cells represented both cue-outcome contingency and time context in which the monkeys experienced the contingency.

The final theory to be discussed in this section is the Medial-Temporal Lobe Conduit for Parallel Connectivity [127]. This theory discusses the hierarchical nature of brain organization at a systems level and is mentioned because it uses the concept of parallel processing in a different manner (i.e., not referring to cortical circuits) than that in relation to the DSM. The lower levels are involved with sensory processing (e.g., sensory and association cortices) and the upper involving frontal cortex (e.g., orbitofrontal). An example of a middle level is the rostral cingulate cortex. The medial temporal lobe serves as a bridge connecting the upper and lower levels by providing a parallel architecture which optimizes information flow. This aids in attention, encoding, and processing of quick complex visual information. Consolidation is viewed as a secondary process that occurs after a medial temporal lobe-bridged connection that eventually allows upper and lower levels to directly access each other. The bridging is purported to allow upper and lower level communication without the need for the intermediate levels of representation.

In summary, the concept of binding has been present in relation to multiple theories of episodic and declarative memory for many years. A major unanswered question in each of the discussed theories involves what exactly is being bound in the hippocampus and cortex, as well as how these are related? The DSM provides a direct answer to that question. In relation to spatial cognition, binding has not been discussed at the same level as it has with episodic memory.

4.   Spatial Cognition

In relation to spatially guided behavior, Selemon & Goldman-Rakic [127] described the efferent projections of the dorsolateral prefrontal cortex and posterior parietal cortex in rhesus monkeys. They found what they termed as "a remarkably large number" of involved areas cortically and subcortically. Based on these findings, they suggested that the involved circuitry for spatial perception might be a set of parallel circuits, each of which controls specific aspects of spatially guided behavior. In relation to hippocampal connections, the parahippocampal cortex and presubiculum were targets. Parahippocampal cortex is connected to the posterior hippocampus in humans and other animals [128]. Based on the multiple level representation of the external world

across the cortical hierarchy, it has been suggested that the peak of the abstraction is the representation of external space in the medial entorhinal cortex and the hippocampus [129].

More recently, Shen et al. [130] found there is large-scale dynamic functional connectivity consistent with structural connections in the macaque. Functional connections within the rich-club core exhibited the greatest stability over time. In a recent study [131] with rats, high resolution fMRI of interconnections to the retrosplenial cortex involved parietal association cortex, hippocampus, thalamic nuclei, midbrain structures, and hypothalamic mammillary bodies. The authors concluded the results support a sensory-cognitive network with a hub in the retrosplenial cortex involved in sensory information, spatial learning, and episodic memory. Thus, there are data supporting distributed processing in the brain for spatial learning.

The first paper to identify hippocampal place cells with the suggestion that the hippocampus serves as a spatial map (to allow navigation based on O'Keefe and Nadel [132]) was by O'Keefe and Dostrovsky [123] in 1971. Specific mechanisms were later discussed [133] on how the map could be read to enable navigation. Problems with the theory [134] have been noted, including findings that place cell firing is influenced by other high-level variables (e.g., running speed) and tuning to low-level properties (e.g., direction being faced). A second problem is that most data supporting place cells are based on rodents and, in primates, hippocampal neurons have been suggested to be spatial view cells [135].

Much later [136] the second distinct external space receptive fields were identified (i.e., grid cells) in the medial entorhinal cortex. Grid cells are place-selective and fire at discrete and regularly spaced locations [129]. In their review on grid cells, Moser et al. [129] indicated that the grid cell map is dynamic based on an animal's movement, and evidence indicates sensory input involves proprioceptive/kinesthetic feedback, in addition to optic flow and vestibular signals. Those authors note that other cell populations (e.g., running speed, head direction) have also been identified in the medial entorhinal cortex. The interested reader is referred to the excellent review article by Moser et al. [129] for a detailed discussion of the possible ways the medial entorhinal cortex and hippocampal place cells may interact, as well as attractor models in relation to the medial entorhinal cortex. However, there remains much debate as witnessed by a recent review article [137] that provided the new suggestion that grid cells encode the geometric layout of enclosures.

In relation to binding, it seems reasonable that the hippocampal cells associated with cortical spatial aspects may function in a similar manner suggested in episodic memory. Specifically, the hippocampus is viewed by the DSM as serving the sole purpose of consolidating memories that involve distributed cortical regions (i.e., the parallel circuits discussed by Selemon & Goldman-Rakic [127]) in the same manner that it is involved in the distributed cortical regions involved in episodic memories.

5.   Application of the Parallel Circuits Binding Model of Hippocampal Functioning

To further facilitate the understanding of this paper's theoretical proposals, it will be contrasted with the Component Process Model [2], which is clearly one of the most sophisticated and highly

developed models of hippocampal functioning. The Component Process Model proposes that the hippocampus forms a memory trace or engram that in an obligatory fashion binds "neural elements" (authors' italics) in the neocortex and medial temporal lobe associated with the multiple aspects involved in a conscious experience. Based on this view, consciousness is linked to episodic memory. The hippocampal component of the bound hippocampal-neocortical ensemble is sparsely coded, being viewed as what they call a spatial scaffold or matrix. This matrix acts as a pointer or index to the various neocortical elements involved in the episodic memory, including the sense of autonoetic consciousness. The storage in the hippocampus is theorized to be random and only close temporal association or contiguity with a reinstated context determines which elements are bound.

In relation to memory retrieval the Component Process Model [2] proposes a two-stage process that occurs based on internal or external cues. The first is an unconscious interaction between the cue and the hippocampus that reactivates the bound neocortical traces. This may lead to a second stage involving a conscious experiencing of the episodic memory. The prefrontal cortex and related structures are viewed by this theory as controlling the obligatorily hippocampus-activated neocortical elements to make memory intelligent and goal directed. In this view the hippocampus is at the top of the hierarchy of the posterior cortical processing in which there is a progression from more basic to integrated information. Additionally, there are back projections allowing the more complex cortical representations to influence the earlier stages of processing. Posterior cortical processing projects to the perirhinal and parahippocampal cortices which in turn project to the entorhinal cortex that projects to the posterior hippocampus. The anterior hippocampus is connected to anterior neocortical structures involving the global aspects of an episodic memory, such as general context, meaning, and emotion.

There are a number of overlaps with the DSM, but several notable differences. The DSM slave view of hippocampal cells is consistent with the obligatory view of the component process model, but our model indicates there is no random storage. It agrees there is sparse coding in the hippocampus, but specific hippocampal excitatory cells correspond to specific cortical column circuits. Specificity is required if the hippocampal cells are responsible for a pacemaker (i.e., reactivating the circuit) role of the cortical consolidation process [6,19]. In this case there can be lower-order component cortical circuits with their respective hippocampal cells, but also the multi-component entorhinal cortex column that has its specific cells in the hippocampus. Although there is close temporal contiguity of the various circuits involved, the DSM indicates it is the successive progression of the cortical circuits activated that project to the medial temporal cortex that determines what aspects are bound as opposed to time itself.

A major difference is how the DSM views autonoetic consciousness. Whereas the Component Process Model views this as a defining characteristic of episodic memory and as a special type of memory, the DSM considers this verbal interpreter [5,6,43] circuit as only one of a number of parallel circuits that can potentially involve the hippocampus. Thus, as in the case of multiple cortical column circuits in a rodent's brain involved in a spatial memory, hippocampal cells serve the same

function in consolidating the spatial memory circuits as they do in humans who form a declarative or episodic memory.

In relation to memory retrieval, the DSM is in agreement with the fact that reactivation of the posterior cortical circuits leads to the activation of hippocampal cells. As stated, the DSM indicates the same hippocampal cells are reactivated each time their associated cortical circuits are activated. However, the DSM indicates it is not the hippocampal cells that lead to the reactivation of the various cortically located aspects of the episodic memory, but actually the frontally located action columns that lead to the aspects being reactivated. As previously noted, for each posterior column the DSM proposes there is a corresponding frontal action column that forms. A higher-order action column has the ability to activate its lower-order columns that correspond to the posterior receptive (e.g., sensory) columns. Thus, instead of what Moscovitch et al. [2] called back projections that allows components to be reactivated, the DSM indicates it is the action columns connected to each of the posterior columns that allows that reactivation. Each of the hippocampal cells that reactivates with the retrieval of an episodic memory is based on that memory's respective associated cortical circuit first being reactivated. As seen, this is consistent with the slave or obligatory function of a hippocampal cell.

As previously discussed and consistent with the Component Process Model, the left ventral frontal region is responsible for verbal awareness of the episodic memory. There are times of parallel circuits' activation in which there is no ability to verbally explain despite the verbal interpreter circuit being involved. For instance, based on our model a drug addict may experience an urge (medial frontal cortex) based on memories of internal or external cues, be verbally aware of the urge, and be unable to verbally describe the specific cue(s) that led to the urge. At the same time the addict may verbally describe the fact a specific place, time of day, or emotion seems to be associated with the urge.

An aspect largely absent in the other theories of hippocampal functioning is related to hemispheric asymmetry. As previously mentioned the left hemisphere involves a greater number of columns in the circuits and the right has fewer. Each hemisphere has its own hippocampus and the concept of consciousness discussed by Moscovitch et al. [2] is restricted to the verbal interpreter circuit's access to the information of other cortical circuits based on the DSM. This access can be direct via its interconnections or indirect. Thus, it is possible that episodic memories can involve circuits to which the verbal interpreter has no access. If accurate, then it is obvious that any theory of hippocampal functioning that has its foundation in one's verbal awareness of associated memories is flawed. Gazzaniga [47] provided several examples of split brain research that clearly shows the fallibility of the left interpreter in accurately describing right hemisphere processing and actually providing explanations that were factually unfounded.

A clinical example involves hypothesized right posterior cortical memory involving the activation of a negative emotional state which often occurs with sympathetically-mediated symptoms. Moss [44] gave an example of a woman who is forcefully held by her wrists during a sexual assault.

At a later time, she was grabbed by the wrist by someone she trusts and experiences a panic/fear response. Based on the DSM, the tactile columns for the wrist lead to the activation of the column circuits where the various right cortical non-detailed (e.g., contextual aspects, voice intonations of the perpetrator, general body size and facial features of the perpetrator) sensory and emotional aspects are represented. The victim is able to verbally state she had a panic attack that logically makes no sense based on the identity of the person who held her wrist. She is unable to describe all of the right hemisphere column circuits that were activated. In fact, the psychological treatment in which the patient verbally describes what occurred with every possible detail recalled over three to four repetitions results in her being able to recall many more specific details in the latter descriptions. As those details are discussed, the verbal interpreter circuit becomes aware as she visualizes those in her right cortex. Thus, she had the memories present cortically with the verbal interpreter circuit remaining unaware. Obviously, there can be other memories present that the victim fails to recall even during the treatment process. The point is that these are clearly episodic memories, but without consciousness as defined by the verbal interpreter being initially involved.

5.1.   Memory transformation

The Component Process Model indicates that episodic memories that retain their highly detailed aspects are dependent upon hippocampal involvement and are recollective. Others can be transformed via forgetting (leading to memories with lost details that retain only a gist or familiarity) or schematization (incorporated into pre-existing schemas). The transformed memories are considered to be more reliant on neocortical structures, specifying the pre-frontal ventral medial and anterior temporal lobe cortices as prominent in this process. Additionally, specific and gist representations can coexist. They place this in the context of what they call a general principle of cognitive neuroscience they call Functional-Neural Isomorphism. Moscovitch et al. [2] explain this is the view that representations that differ from one another are mediated by different structures involving collections of neurons. Thus, representations mediated by different structures must differ in some fundamental way from one another.

At the level of cortical processing the DSM disagrees that there are any fundamental differences. As was explained, column circuits are the same and the qualitative difference occurs based on the information represented by different columns. Additionally, the hippocampus is not actually involved in the recollection of specifics since the DSM ascribes this to frontal action columns. However, it was previously discussed how the DSM views the hippocampal cells as facilitating both association and consolidation of new circuits with pre-existing column circuits and, as such, strongly contribute to the transformation process of schematization. The DSM explanation of forgetting and memory transformation was also previously discussed. Moscovitch et al. [2] suggested that all the components of the hippocampus, neocortex, and other structures involved in an episodic memory do not necessarily comprehensively get activated at the same time or in all tasks. They introduce the

concept of Process-Specific Alliances in which only the necessary components activate based on task demands. The DSM is certainly consistent with this concept as described in the foregoing sexual assault example. However, Moscovitch et al. [2] go on to discuss four assumptions in their updated Component Process Model. These assumptions highlight differences in our respective models.

5.2. Assumption 1

The Component Process Model indicates that during perception there is a progression of increased complexity of information representations from early to late sensory and medial temporal lobe regions. The complex events binding objects to spatiotemporal contexts and feeling of experience purportedly occurs in the hippocampus. Although the DSM agrees that the hippocampus is necessary for binding and provides the exact manner that sensory information proceeds from lower-order to higher-order columns, there are several other aspects to be considered. In the case of one or multiple senses being involved, then there is bilateral activation of the primary sensory cortices in the hemispheres. Thus, there can be multiple cortical circuits (e.g., dorsal, lateral, and ventral directions from visual cortex) from each of the primary sensory areas involved. The posterior lobes' cortical circuitry can activate subcortical structures (e.g., amygdalae) involved in the physiological responses associated with emotions [138]. Posterior columns also immediately activate their respective frontal columns. The various posterior parallel cortical column circuits' highest-order columns project to the medial temporal lobe cortex (i.e., perirhinal, parahippocampal, entorhinal) and it is there that the DSM says exist the columns that are actually the most complex representations, not the hippocampus.

5.3. Assumption 2

The Component Process Model indicates the same regions activated during perception remain active for a while due to top-down modulation from the prefrontal cortex. This permits the persistence of the object and contextual representations, as well as the unified event representations, within working memory. The DSM is consistent with this aspect, but specifies the frontal mechanisms that allow this process involve previously developed columnar circuits. For example, when there is the conscious (i.e., verbal interpreter circuit) decision to recall information, there is established circuitry tied to the intent and the action of verbal labeling/describing (i.e., left frontal ventral medial to left frontal ventral lateral to dorsolateral cortices), in conjunction with the newly formed frontal action columns based on the posterior receptive cortical columns that are activated with the specific events. An example of right cortical working memory is when the act of visualization occurs with memory recall (i.e., right frontal ventral medial to right frontal lateral to dorsolateral). In both cases the newly formed frontal action columns reactivate their respective posterior receptive columns that create the re-experiencing of the various aspects of an episode.

5.4.   Assumption 3

The Component Process Model stipulates that during encoding a fraction of the transient representations in working memory are transformed to a long-lasting format in the cortex and hippocampus. The hippocampus representation points to the location of cortical memory traces, a hippocampus-to-cortex Process-Specific Alliance. It is further explained that the encoding process is supported by an anterior hippocampus-ventral medial prefrontal Process-Specific Alliance mediating schematic relational processes and a medial temporal lobe-ventrolateral prefrontal cortex Process-Specific Alliance mediating semantic processes.

It has been discussed how the DSM differs in that the hippocampus is not involved in pointing to cortical circuits (the DSM attributes this to frontal action columns which lead to posterior circuit reactivation and increased probability of consolidation via reactivation of the circuit's hippocampal cells). The role of the hippocampus in consolidating new circuits, as well as their association with pre-existing circuits (e.g., schematization), has also been discussed.

5.5.   Assumption 4

Based on the Component Process Model, during retrieval access to the integrated event representation in the hippocampus is responsible for the reactivation of the medial temporal lobe and posterior cortices associated with the memory traces and awareness of the recollected memories. Moreover, the retrieval processes are supported by the prefrontal cortical cortex control processes. The authors [2] make a final statement that oscillatory mechanisms are assumed to contribute to all the processes described in the four assumptions.

The DSM clearly indicates the only role the hippocampus serves in connection to both the posterior and associated frontal parallel cortical column circuits is for consolidation. Thus, there is reactivation of the circuits, but not for retrieval/awareness purposes. Based on the DSM [6,19], gamma frequency oscillations are part of the previously discussed process associated with the dynamic formation of each column. One other aspect not fully discussed is the theorized mechanism by which hippocampal cells influence consolidation. This involves simultaneous VIP activation leading to disinhibition of all associated cortical columns of the complex memory and this is not in a feedforward fashion. This allows all columns in the circuit to become phase-locked. There is no feed-forward activation that occurs in the circuit which is required for both the retrieval and the awareness of the memory to occur. The DSM indicates that the frontal columns are necessary for the reactivation of the posterior columns in a feed-forward fashion associated with retrieval and verbal awareness (provided the verbal interpreter circuit is involved). Thus, the frontal cortex is solely responsible for one's intentional recall (i.e., top-down) of an episodic memory. Additionally, internal and external cues can lead to the feed-forward reactivation (bottom-up) of various aspects of an episodic memory.

A final aspect is that the DSM suggests cortical interneuron GABA has the primary role of dynamic column formation, whereas basal ganglia GABA provides inhibitory functions for the circuits of cortical columns [43,44]. Although not required for serial circuit consolidation, the hippocampus can support reentrant and thalamic-cortical consolidation processes. This is at the new column level to assist in consolidating the minicolumns defining the column boundary and at the circuit level to strengthen synaptic connections among columns in the cortex and with subcortical structures. However, hippocampal involvement is mandatory for the binding of parallel circuits.

6.   Conclusions

The current paper has discussed the proposal that the hippocampus serves the uniform function of binding parallel cortical column circuits. An obvious position is that the role of the hippocampus can only be appreciated within the context of a general model of cortical processing. Although information has been discussed in support of this novel view, only through *a priori* studies can the validity of this theory be determined. In conclusion, it is hoped the current theory that supports the view that the hippocampus is a complex structure with an elegantly simple function will stimulate such research.

Conflict of Interest

Author declares no conflicts of interest in this paper.

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