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A possible mechanism of transfer of memories from the hippocampus to the cortex

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ABSTRACT

The mechanism of time-dependent transfer of memories from the hippocampus to the cortex associated with the memory consolidation process still remains unknown. By visualizing memory as the virtual sensation of sensory stimuli, it has become possible to conceptualize memory as an integral of semblances induced at the postsynapses in the absence of the activation of their corresponding presynapses. This is hypothesized to be possible during memory retrieval by the re-activation of functional LINKs formed between the postsynapses during learning. On occasions of repetition of learning, related learning and unrelated learning, stimulation of the sensory receptor pairs used in the original learning event activates new hippocampal neurons incorporated in the circuitry and induces formation of new functional LINKs in the cortex. Since the virtual sensory units of semblances provide provisions for the formation of similar net semblance from different sets of postsynapses of origin both independently and cumulatively, locations of their formation appear transferable. When semblances from the cortex alone become sufficient to contribute to a specific memory, after a certain period of time from the initial learning, removal of the hippocampus gives an impression of (an apparent) transfer of memories from the hippocampus to the cortex.

Introduction

The mechanism of memory storage and retrieval at physiological time-scales remain a challenging subject. Theoretical examination of various findings associated with memory may provide us valuable information about the mechanisms. One of the challenges is to discover the mechanisms for the observation that memories change locations of their storage as they become more stabilized. The present work examines whether the following two parallel time-dependent changes occurring during consolidation may be related. One is the integration of thousands of new granule neurons every day into the hippocampal circuitry [1,2] without the removal of the old ones. The second is the time-dependent transfer of memories from the hippocampus to the cortex responsible for the consolidation process, that was extensively studied in the patient H.M. [3], whose medial temporal lobes (including the hippocampi) were removed in a therapeutic surgical procedure. Evidence for changing locations of memory storage from the hippocampus to the cortex during consolidation was reported in various experiments [4–6]. Systems consolidation provides details about how memories are engrained for long-term storage through the transfer of memories to the cortex [7–9].

New neuron formation from stem cells in the adult hippocampus [10] and the integration of thousands of these new neurons daily into the circuitry [11] without removal of the old ones [12] have inspired many questions about their functional roles. Enriched environments that have the potential to promote various types of associative learning induce more adult hippocampal neurons [13]. Various studies have shown the importance of hippocampal neurogenesis in spatial memory [14–16] and cognitive abilities [16]. One study demonstrated the prolonged need for the hippocampus in the expression of remote contextual memories [17], supporting the idea that the hippocampus is involved in the integration of new information into existing extra-hippocampal networks [18]. In a recent study, the hippocampus-dependent period of associative fear memories was found to be modulated by adult neurogenesis [19]. More importantly, the observation of reduced clearance of hippocampal memory traces in mice deficient in neurogenesis [20] indicates that neurogenesis is required for the transfer of memories from the hippocampus to the cortex.

Recent reviews of the functional role of adult neurogenesis [21,22] have discussed various theories investigating the role of new neurons in learning [23–27]. The neurogenic reserve hypothesis [28] has examined the role of new granule neurons in adaptation to novel and complex environments. Even though studies were carried out to substantiate the role of granule neurons in increasing memory specificity, their role in the consolidation of memories is considered a difficult problem [22]. In this context, the present work examines a feasible mechanism that may have the potential to explain the possible role of new neurons in various

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functional aspects of memory storage including the consolidation of memories.

Background

The basic issues associated with explaining the consolidation process concern the fact that it is not yet known how memories are stored and retrieved. Alternatively, memory storage mechanisms should be able to support the consolidation process whereby memories can be transferred from the hippocampus to the cortex over a long period of time. The first challenge here is to explain a feasible mechanism to demonstrate retrieved memories as virtual sensations representing sensory stimuli occurring in their absence. How can we explain the virtual sensation during memory retrieval in terms of cellular neurobiological changes? Here, we first examine the available resources; next we build a theoretical framework that can satisfy the required features. It has been suggested that there are two different types of time-dependent memory stabilization processes, namely synaptic consolidation that lasts for hours and systems consolidation that may last for years [29]. These stages are essential in building representations of memory that can be used to explain consolidation. The main challenges involve in building hypotheses are relating the cellular changes to explain a virtual sensation and its transfer of locations within the nervous system over time. This will require the usage of feasible assumptions at few instances that need to be tested though empirical research.

It has not been possible to show either the time-scales or the mechanisms of retrieval of memories as different for different types of memories. The present work has incorporated various features satisfying both memory storage and cognitive capabilities [30,31]. These include provisions for unlimited life-times of memories, absence of overwriting of old memories with new ones, absence of decay of the memory trace by any modifications of the basic units by new learning, sparseness without reduction in information storage, instantaneous access to very large memory stores, the ability to generate hypotheses, and the capacity for interaction between internally generated hypotheses and external evidence that allows sensory data to reject or support internal constructs extremely efficiently.

What is unique about the hippocampus that makes the transfer of hippocampus-dependent memories to the cortex possible? (1) The hippocampus is a location where direct olfactory inputs and processed multiple sensory inputs [32] converge. (2) The hippocampus is also one of the brain regions where continuous neurogenesis takes place and has been shown to be essential for spatial memory [12]. The consolidation of some form of hippocampus-dependent memories is substantiated by neuropsychological and behavioral tests conducted after the removal of hippocampi, both in the humans and animals [3–5].

Knowledge of the representation of memory is required to understand what is being transferred from the hippocampus to the cortex during consolidation [33], the effect of recall upon the memories themselves, the stabilization after retrieval following initial consolidation, a process called reconsolidation [34,35], the role of proposed mechanisms beyond consolidation [36], the stability of the engram [37,38], and slow learning by the neocortex [37,38]. Viewing memories as virtual sensations of sensory stimuli provides the advantage that no connecting neurons are required from the point of origin of the virtual sensations to the sensory receptors that were activated by the learned item during the initial learning event. Provided a surplus of interchangeable origins is available, it may be possible to use them interchangeably to achieve a threshold form of retrievable memory. Based on a hypothesis where memories are viewed as virtual sensations of sensory stimuli, namely the semblance hypothesis [39], the present work explains possible mechanisms of consolidation of memories using hippocampal new neurons and are explained under the following sections. (1) Semblance formation as a basic unit that explains memory as a virtual sensation of sensory stimuli occurring at physiological time-scales, (2) time-dependent transfer of memories from the hippocampus to the cortex, and (3) retrieval of cortically-stored memories following the removal of the hippocampi.

Hypothesis

Semblance formation at physiological time-scales

First, we will examine the elements that are required at the synapses at various orders of neurons (the first order of neurons is the one that receives inputs from sensory stimuli) that can synthesize a framework of a virtual sensation of sensory stimulus at the time of memory retrieval. The basic framework was derived from the argument that the re-activation of a specific subset of synapses that was activated during learning can induce memory. The activation of a postsynapse (postsynaptic terminal or dendritic spine) takes place when neurotransmission occurs from the presynapse (presynaptic terminal). Therefore, activation of the postsynapse can be taken as the minimum requirement to determine when one synapse is activated. During learning, the co-activation of the postsynapses from the cue-stimulus and the learned item is hypothesized to induce specific changes that will later allow the cue-stimulus alone to evoke the activation of a subset of postsynapses that creates representations of the learned item.

At locations where higher orders of neurons from the cue and the learned item converge, the postsynapses are expected to be spatially close to each other in order to induce the above changes. These are locations where multiple sensory inputs converge; for example, the hippocampus. When activity reaches the postsynapses from both the cue and the item to be learned at these locations, a transient functional LINK (capital letters are used to denote its significance) is expected to form between these postsynapses and is viewed as a function of the simultaneous arrival of activity at both the postsynapses (Fig. 1a). During memory retrieval, the arrival of excitatory postsynaptic potential (EPSP) at one of the postsynapses is expected to induce the re-activation of this functional LINK, evoking changes in the second postsynapse reminiscent of the arrival of activity at the latter's presynaptic terminal (other possible mechanisms are also explained [39]). Activating a postsynapse without the activation of its presynaptic terminal is expected to evoke the cellular hallucination of an action potential-induced synaptic transmission from its presynaptic terminal. This is called synaptic semblance (Fig. 1b).

In this and next paragraph, the depth of the cellular hallucination occurring at postsynapse D is assessed to understand its sensory equivalents. Semblance formed at postsynapse D (in Fig. 1b) gives the cellular hallucination of an action potential reaching at presynapse C that belongs to neuron Z. Neuron Z, in turn, can only be depolarized by activating a set of axonal terminals of the neurons that synapse to the dendritic spines (postsynapses) on its dendritic tree. Spatial summation of EPSPs from nearly 40 or temporal summation of EPSPs from much less than 40 postsynapses at the soma triggers an action potential. Since it is possible that activity from a large number of possible combinations of inputs arriving at Z's nearly $2.4–8 \times 10^4$ dendritic spines [40] has the capability to trigger the same action potential, we can now say that the cellular hallucination occurring at postsynapse D could indicate a hallucination of activity coming from the above combination of inputs.

The set of all the combinations of neurons {Y}, whose axonal terminals can induce action potential of neuron Z can be

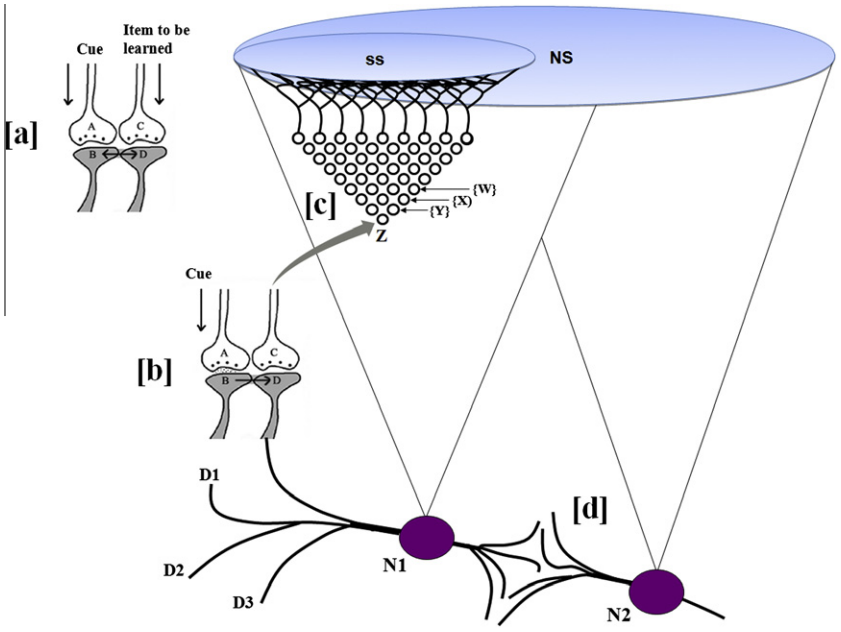

Fig. 1. Schematic representation of the formation of net functional semblance from synaptic and network semblances during memory retrieval. [a] Illustration showing the hypothesized functional LINK formation between the two postsynaptic membranes B and D during learning. The functional LINK is transient and its formation is a function of the simultaneous activation of the postsynapses B and D. A and C are the corresponding presynapses. [b] During memory retrieval, the cue-stimulus reaching presynaptic terminal A depolarizes its postsynaptic membrane B and the resulting EPSP at postsynapse B re-activates the functional LINK that activates postsynaptic membrane D (mechanisms other than depolarization are also discussed [39]). When postsynaptic membrane D is depolarized, it evokes the cellular hallucination of an action potential reaching its presynaptic terminal C. This is called synaptic semblance. [c] Representative account of the quality of the sensory stimulus that postsynapse D is hallucinating about. To identify this, we must know all the sensory receptors that can contribute towards the activation of postsynapse D. Normally, neuron Z to which presynaptic terminal C in figure [b] belongs, receives activity from a set of lower order of neurons {Y}. This set of neurons {Y} is in turn is activated by another set of neurons {X} in the penultimate neuronal order. By extrapolating the penultimate lower orders of neurons, from which a higher order neuron can receive activity, in a retrograde fashion we reach the sensory receptors. The final potential sensory receptor group is represented by the small elliptical shape (marked as ss), that denotes the sensory feature of synaptic semblance. Activation of the sensory receptors from this sensory receptor group is expected to contribute to the activation of the presynaptic terminal C in figure [b] (provided background neuronal oscillatory activity at certain defined neuronal orders in the hippocampus and cortex contribute sufficient EPSPs at the axon hillock of the intermediate neurons finally activating the neuron Z). Synaptic semblance at postsynapse D refers to the hallucination of activation of the sensory receptor group ss. [d] EPSPs from the postsynapses similar to D in figure [b] (D_1, D_2, and D_3 shown in the diagram) summate and become capable of triggering an action potential at the axon hillock of the neuron N1, which creates representations of the learned item. This neuron N_1 in turn can activate a network of neurons downstream from it (here only one representative neuron N_2 is shown). Firing of the first neuron N_1 activate a network of neurons, which creates representations of the learned item. Firing of neurons without activating their normally activating neurons induces network semblance (represented by the large elliptical shape marked as NS). The sensory identity of the cellular hallucination during the network semblance is determined by an approach similar to that of the retrograde search for sensory meaning of synaptic semblance (figure was used after modification [39].

determined from the existing functional connections that the set of neurons {Y} make with the neuron Z. Each neuron connected to the neurons in the set {Y} in turn receives functional connections from a set of all the possible combinations of neurons upstream from the set of neurons {Y}. Let this set of neurons be {X}. By moving in a retrograde fashion towards the sensory level, the sets of neurons at each of the preceding neuronal orders whose activity forms part of the hallucination at postsynapse D can be determined. The last step of this process will be to determine the set of sensory receptors whose activation can theoretically cause the activation of presynapse C (Fig. 1c). In other words, the identity of the sensation being hallucinated at postsynapse D is determined by the set of these sensory receptors. The hallucination at the postsynapse D is evoked by the re-activation of the functional LINK from postsynapse B which, in turn, is activated by the cue stimulus. Thus, specific synaptic semblances elicited (through the functional LINKs at the synapses) from all the neuronal orders in response to a specific cue stimulus can be integrated to obtain the net functional semblance, which is memory. Net functional semblance beyond certain threshold value may have only minimal influence on the quality of the memory. The exact nature of the integration process needs to be studied.

In addition to triggering action potentials in many neurons, background neuronal oscillations and the continuum of sensory inputs that the nervous system receives lead to the summation of EPSPs in many neurons to only sub-threshold levels short of eliciting action potentials. In this context, the arrival of the specific cue stimulus can re-activate many functional LINKs to activate postsynapses and trigger action potentials in many of these neurons that are activated at sub-threshold levels (neurons N1 and N2 in Fig. 1d) that creates representations of the learned item. These action potentials may propagate in the downstream network of neurons that also creates representations of the learned item, which in turn creates the hallucination of receiving a subset of sensory inputs from the learned item. From identifying these cue-activated networks of neurons that represents the learned item, semblances of sensory identity can be calculated similar to the approach used in finding synaptic semblance in the above paragraphs. These semblances are called network semblances (Fig. 1d).

According to the present hypothesis, activity at one of the postsynapses can re-activate the functional LINK between the LINKed postsynapses. Therefore, when extrapolation is made from a synapse or a neuron to estimate the semblances, both the synaptic connections and functional LINKs formed prior to the memory retrieval need to be taken into account.

Representations of memory

Let the set of all the specific postsynapses and neurons that are activated by an item to be learned before learning be {P} and {N}, respectively. Let us imagine that associative learning takes place between the item to be learned and a specific cue stimulus inducing functional LINKs at a subset {p} of the set of postsynapses {P}. During retrieval of memory in the presence of the specific cue

stimulus, the re-activation of the functional LINKs is expected to activate a subset {p1} of the set of postsynapses {p} inducing synaptic semblance and activate a subset {n} of the set of neurons {N} inducing network semblance. Due to a delay in neurotransmission at the chemical synapses, the semblances from each neuronal order take place in a temporal order. The cue stimulus-induced simultaneous semblances generated at the synapses at each order of neurons (by combination) and the temporal formation of semblances (due to synaptic delay) at different orders of neurons (by permutation) can be integrated to form the multi-dimensional virtual sensation of a sensory stimulus, which is memory (Figs. 1c and d).

Non-requirement of neuronal connections from the postsynapses towards the sensory receptors for the formation of semblances

Semblance at postsynapse D is viewed as a virtual sensation by virtue of the hallucinations created by the activation of postsynapse D without activating its normal presynaptic counterpart C. This formation of a virtual sensation during semblance formation can be considered an essential feature of the nervous system and can possibly explain many sensory phenomena; for example, memory and phantom limb. It also explains why the physical presence of the initial orders of neurons from their sensory receptors activated by the learned item is not required at the time of memory retrieval. Since net semblance is a virtual sensation, it is also viewed as a property of the internal state of the nervous system. Note that the neuronal connections from cue stimulus to postsynapse B that connect postsynapse D through a functional LINK are required for re-activating the functional LINK to induce semblance.

Gradual transfer of representations of memory from the hippocampus to the cortex

Repetition of learning at optimal intervals

The neurons generated at the sub-granular zone of the hippocampal dentate gyrus extend their axonal terminals to form synapses with the CA3 neurons and their dendritic processes to form synapses with the neurons in the molecular layer [41,42]. Since thousands of new neurons are formed every day [11], it is reasonable to expect that an almost equal number of new neurons are integrated into the circuitry on a daily basis. Repetition of learning is likely to re-activate all the existing functional LINKs between the postsynapses at different neuronal orders formed during prior learning (pathway 1). In addition, based on the rate of neurogenesis in the hippocampus, repetition of learning after an optimum interval is likely to induce activation of some of the new hippocampal neurons, their newly formed connections (Fig. 2) and, by necessity, all these connections' pre-existing functional LINKs at the higher orders of neurons (pathway 2). Therefore, during the repetition of learning, new functional LINKs form between the postsynapses belonging to the pathways 1 and 2 (not shown in figures). This will lead to the formation of additional semblances during memory retrieval after repeated learning, compared to the retrieval of memories after the initial learning. Similar effects can also occur if many related items are learned after the initial learning event. In summary, the repetition of learning or related learning will contribute to replaceable alternate semblances for a specific memory.

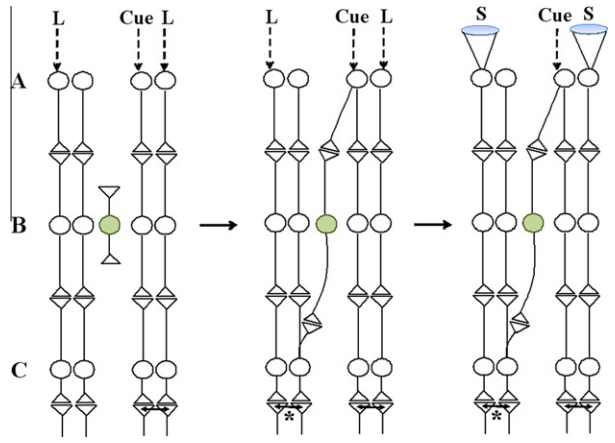

Fig. 2. Role of neurogenesis in the hippocampus in inducing a functional LINK between postsynapses in the cortex. *Left panel:* learning occurring before a new neuron (green cell body) establishes synaptic connections inducing the formation of a functional LINK. *Middle panel:* new neuron establishes synaptic connections such that the simultaneous activation of the receptors from the cue and the learned item induces a new functional LINK (marked by an asterisk) in the cortex. *Right panel:* the cue-stimulus activating its receptor (marked as belonging to the line A) now induces the semblance of activity arriving from two receptors that were activated by the learned item. A: first order of neurons from the sensory receptor level. B: Hippocampus. C: Cortex. L: Item to be learned (figure was used after modification [39]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

At this stage we assume the following. (1) New semblances can be added to the existing net semblances for an item without affecting the qualities of the retrieved memories. This assumption may guide the application of required parameters for the computational studies. (2) The physical qualities of the semblances except the strength may remain unaffected irrespective of their origin. (3) Once sufficient net semblances are formed from using functional LINKs, the excess semblances can be removed. In other words, the origins of semblances are degenerate or interchangeable with regards to obtaining the net functional semblance. (4) Since it is the net semblance above a certain threshold that specifies the sensory identity of the retrieved item (Fig. 6A), postsynapses contributing to excess semblance can be removed (Fig. 6C) without loss of memory. So when the representation of memory in the cortex exceeds the threshold of semblance required for memory retrieval, memory can be retrieved even when the hippocampus is removed. This framework is in agreement with the evidence of wide distribution of memory throughout large brain regions [43], variations of memory storage locations among individuals [44] and the suggestions of the presence of complementary learning systems in the hippocampus and neocortex [38].

Unrelated learning activating the sensory receptors used in the initial learning

The number of sensory receptors in an animal is finite. Many pairs of sensory receptors used in one associative learning event are also used in different related or unrelated associative learning events. Let the cue stimulus activate X_n receptors and the learned item activate Y_n receptors in an associative learning event. Let X_1 and Y_1 be representative subsets of these receptors (Fig. 3). Let the activation of receptor X_1 pass through the extra-hippocampal pathway to the higher cortical neurons and let the activation of receptor Y_1 pass through the hippocampus. Since the sensory receptors are limited in number, the sensory receptors X_1 and Y_1 will be used for many different associative learning events during the life of an animal. Let us assume that during one learning event functional LINKs are formed between the postsynapses of the neurons in the cortex from the receptor subsets X_1 and Y_1 (Fig. 3).

Simultaneous activation of X_n and Y_n receptors during any future learning will increase the number of functional LINKs between their activated postsynapses in the cortex due to the effect of expansion of the circuit by the incorporation of new neurons in the hippocampus as explained in Fig. 3. The activation of different

subsets of receptors from the set of X_n and Y_n receptors occurs during different learning processes. Repeated activation of receptor pairs from X_n and Y_n, at optimal intervals will induce gradual increase in the number of functional LINKs between the postsynapses in the cortex (Figs. 4A and B). Once the cortex builds enough functional LINKs to provide sufficient semblance for memory retrieval, all by itself, (Fig. 4C), a specific memory can be retrieved by the cortex even in the absence of the hippocampus, a process that can be visualized as the transfer of memories from the hippocampus to the cortex. For this to be possible, when hippocampus is removed, sufficient number of extra-hippocampal pathways should be available to re-activate sufficient number of functional LINKs in the cortex for semblance.

The probability of the receptor pairs X_n and Y_n being used in any learning is maximal when associative learning takes place between a cue and a learned item activating all the X_n and Y_n receptors, respectively. Since all the receptor pairs X_n and Y_n are activated during the original associative learning event, this suggests that repetition of learning (at optimal intervals to utilize an optimum number of new neuronal connections) using the same cue and learned item produces maximum retrievable memory storage. The above-demonstrated time and hippocampal neurogenesis-dependent transfer of representations induced by unrelated learning is a mechanism for the transfer of memories from the hippocampus to the cortex.

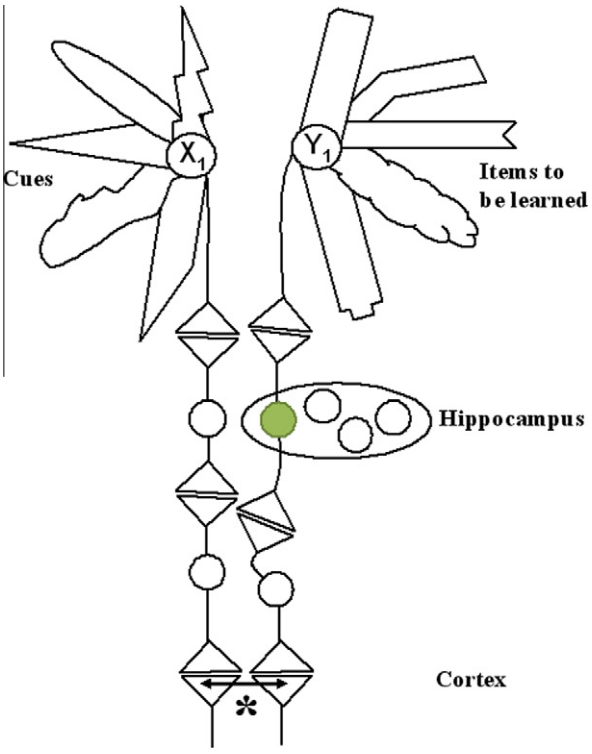

Fig. 3. New functional LINK formation through new neurons activated by sensory receptors that are shared by different cues and learned items. Sensory receptor X_1 is shared by five different cues (represented by different shapes). Similarly, sensory receptor Y_1 is shared by five different learned items. It is assumed that associative learning between the two sensory receptors X_1 and Y_1 has already taken place, inducing functional LINKs that are not shown in this diagram. Let us imagine that repetition of learning takes place after the introduction of a new neuron (green circle) in the hippocampus. Activation of the receptor Y_1 is shown to be transmitted through the new neuron in the hippocampus inducing a new functional LINK (marked by an asterisk). Activation of any of the five cues that activate the receptor X_1 will now induce semblance for the sensory receptor Y_1 through the newly formed functional LINK in the cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A recent study has observed that the blockage of neurogenesis results in memories remaining hippocampus-dependent during a period when the transfer of memories to the cortex could have taken place [19]. This indicates that net semblances achieved by a certain number of new neurons through the reactivation of receptor pairs can be achieved during a short period of time by increasing the number of new neurons under the experimental conditions. These new neurons are expected to activate a subset of receptor pairs from the sensory receptor pairs X_n and Y_n that are activated by the learned item during the initial learning event.

Repeated retrieval of memory

During the retrieval of memories at an optimal interval, two events can occur. One, the cue-stimulus can activate a partial network that creates representations of the learned item. Two, the cue-stimulus can also activate some of the new granule neurons integrated into its circuitry, activating additional neuronal pathways at the higher order of neurons. Activation of these two neuronal pathways will lead to the formation of new functional LINKs between the postsynapses of the neurons belonging to the two above-mentioned pathways (Fig. 5). When the cue is presented again at a later occasion, it will re-activate the new functional LINKs formed during the earlier retrieval events and induce additional semblances, increasing the efficiency of memory retrieval. This supports the proposal that upon each occasion of memory retrieval, a new trace may be created by the hippocampus regardless of the age of the memory [45,46]. This also substantiates the view that memory is reconstructive at the time of retrieval [47] and older re-activated memories become more resistant to disruption [48].

A previous study showed that repeated retrieval produces a large positive effect on the long-term retention of memory [49]. This indicates that repeated retrieval re-activates and stabilizes the functional LINKs made during the initial learning. In another study [50], re-exposure to the odor-cue that was presented as context during prior learning in humans during slow-wave sleep improved the retention of hippocampus-dependent declarative memories, possibly by re-activating the functional LINKs. The establishment of new functional LINKs in the cortex with each memory-retrieval event (at an optimum interval) by new hippocampal neurons incorporated in the circuitry increases net semblances formed from the cortex and improves memory retrieval. This increase in the semblances from the cortex, which permits the removal of hippocampus without losing the net semblance required for memory retrieval, may be interpreted as gradual transfer of locations of memory storage from the hippocampus to the cortex. This can be considered to be another mechanism contributing to the transfer of memories from the hippocampus to the cortex.

Formation of new functional LINKs during reconsolidation

Based on the concept of semblance formation, the consolidation of memories is achieved when the number of net functional LINKs in the cortex alone exceeds the threshold required for efficient memory retrieval; it may not take into account the location of formation of these semblances. If a sufficient number of functional LINKs between the postsynapses in the cortex induced by learning until consolidation is complete remains functionally active to induce threshold net semblances for memory retrieval, then memory retrieval may remain stable. The retrieval of memories after an interval from achieving consolidation is known to induce reconsolidation of memories [34]. Since systems consolidation is a slow process, many new granule neurons would have already formed and been integrated into the hippocampal circuitry before the

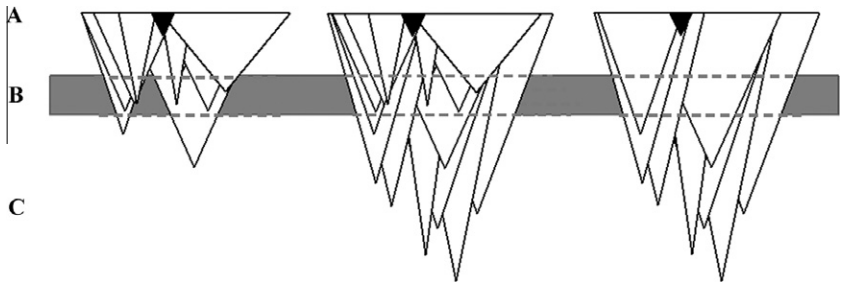

Fig. 4. Hippocampus can be spared when the net semblance from the cortex is above the threshold semblance required for memory. The horizontal bars (A) represent the sensory level. The horizontal rectangular box (B) represents the hippocampus. The area (C) represents the cortex. The triangles show semblances from individual postsynapses. The dark triangle shows the net semblance for the item to be retrieved. The left panel shows semblance formation during retrieval immediately after learning. Most semblances are shown to occur at the hippocampus and a few at the cortex. The middle panel shows increased semblance from the postsynapses in the cortex resulting from repetitions of learning involving the same item or related items or activation of the same pair of sensory receptors. The right panel shows that in the absence of hippocampus (represented by the lack of vertices of triangles in box. B), semblances from the cortex form sufficient net semblance required for memory retrieval (figure was used after modification [39].

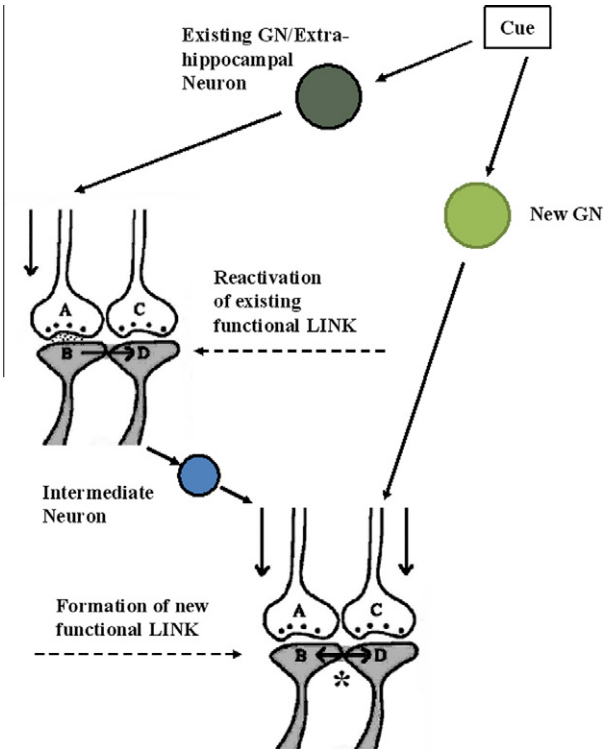

Fig. 5. Schematic representation showing the formation of a new functional LINK during repeated memory retrieval. Cue stimulus activating the existing granule neuron re-activates the already existing functional LINK between the postsynapses in the top pair of synapses in the cortex. The cue stimulus activating a new granule neuron results in a new functional LINK (marked by an asterisk) formation between the postsynapse of its direct synapse and the postsynapse that is re-activated through the previous pathway. In conditions where large number of new functional LINKs are formed in the cortex, they will increase the net semblance in the cortex during memory retrieval, a result of the consolidation of memory. GN: Granule neuron.

event of memory retrieval that evokes reconsolidation. Since retrieval of memory using the old cue will activate many new neurons integrated into the pathway and, by necessity, their higher order neurons, it is possible that many new functional LINKs will be formed between the postsynapses belonging to these two circuits (Fig. 5).

In a continuous learning process, one postsynapse forms additional functional LINKs with other postsynapses that have already made functional LINK with other postsynapses. When this process continues, a cluster or islet of functionally LINKed postsynapses forms (Fig. 6A and B). The new functional LINKs formed during new learning as well as through the activation of new granule neurons during repetition of learning remain at the periphery of an islet (these are to be viewed as functional: not structural entities) of functional LINKs (Fig. 6C) and are expected to be weak LINKs. Most of them may be reactivated immediately after learning providing net semblances for working memory. However, many functional LINKs at the periphery of an islet of LINKed postsynapses are likely to lose their functional LINKs following learning. Those functional LINKs that are often used in associative learning or memory retrieval will move towards the center of the islet of the functional LINKs.

The formation of new functional LINKs during reconsolidation has an effect equivalent to new learning, which supports previous reports that reconsolidation mediates the strengthening of memories by additional learning [35]. Since these new functional LINKs are likely to remain at the periphery of the islets of functionally LINKed postsynapses (Fig. 6), many of them are likely to get destabilized over time if they are not re-activated. Specificity of the reconsolidated memory when induced by the original cue stimulus may depend of the following. (1) During reconsolidation, postsynapse activated by the original cue stimulus may become LINKed to at least one of the postsynapses of an islet of functionally LINKed postsynapses leading to production of non-specific semblances during memory retrieval. Induction of non-specific semblances may dilute specific semblances required for specific memory retrieval. Since the neighborhood postsynapses can vary from islet to islet, the spread of EPSP from one postsynapses of an item is unlikely to induce one specific unrelated semblance to compete with an anticipated semblance of great strength reducing the specificity of the retrieved memories. (2) The ability to spread to functionally LINKed postsynapses in islets enables the formation of semblances to a novel cue, which may get integrated to sufficient strength for evoking novel responses, providing survival advantage to the owner of the nervous system. This can have functional significance in a nervous system with a limited number of sensory receptors and synapses.

Unrelated learning can re-activate and maintain the functional LINKs

Unrelated learning can cause the re-activation of the functional LINKs by mechanisms other than by the activation of the same receptor pairs (Fig. 3). It is possible that the re-activation of any one of the functional LINKs that interLINK the postsynapses within an islet can induce the spread of EPSP to the neighboring postsynapses. This enables the activation of one postsynapse by other

postsynapses, within the islet (Fig. 6C), that were not directly co-activated during any specific associative learning event. Thus, completely unrelated learning events that may re-activate a functional LINK through other functional LINKs within an islet can contribute to formers active maintenance.

A recent study has clearly shown that increased neurogenesis due to running exercise speeds up consolidation of memories [19]. The contributing factors for the observed fast consolidation may include: (1) maintenance of the functional LINKs made by the initial learning by the spread of activity in the expanding (due to neurogenesis) islet of functional LINKs both in the hippocampus and cortex. (2) Increased formation of new cortical functional LINKs by utilizing the additional new neurons (Figs. 2 and 3).

Retrieval of cortically-stored memories after the removal of the hippocampus

The transfer of memory from the hippocampus to the cortex involves gradual increase in the semblances for memory in the cortex. Once functional LINKs in the cortex rise above the threshold number required to produce sufficient semblances for memory, memory can be retrieved from the cortex alone. The formation of specific functional LINKs in the cortex can be elicited by the activation of extra-hippocampal pathways over time; this process mimics transfer of memories from the hippocampus to the cortex. The functional capability of the cortex alone for memory retrieval can only be tested by removing both hippocampi. The patient H.M. who had undergone surgical excision of both hippocampi enabled examination of this process [3]. The patient H.M. suffered memory loss for the events that were learned in the recent years prior to the surgical removal of the hippocampi. When the strength of net semblances elicited through activation of extra-hippocampal pathways alone exceeds the strength of net semblances required for effective memory, memory is retrieved even in the absence of the hippocampus (Figs. 4 and 7). This may explain how the patient H.M. was able to remember associatively-learned remote events.

As discussed earlier, the formation of semblances that provide the virtual sensation of a sensory stimulus to the internal state of the nervous system does not require neuronal connections between the location of semblance and the sensory receptor locations that would have activated by the item whose memory is retrieved. This ability enables the formation of net semblance without stipulating any specific requirement for the origin of the semblances. In other words, this property allows the formation of memories from the combined semblances from the hippocampus and cortex initially and later by semblances from the cortex alone (Figs. 4 and 7). This is seen as the transfer of memories from the hippocampus to the cortex responsible for the consolidation process.

It is possible that integrated net semblances may take such a form that, when associative learning induces functional LINKs in surplus, some of the surplus semblances can be removed without loss of memory. This is also true if we block further neurogenesis. This can explain why spatial memory does not become defective when neurogenesis is reduced with anti-mitotic drugs or irradiation [51,52]. This can also explain reduced fragility of the spared memory in mice with more extensive pre-operative experience in the training environment [53,54]. Based on semblance formation, extensive pre-operative experience will provide receptor pair activations inducing functional LINKs and granule neuron integration which in turn further increases the number of functional LINKs in the cortex prior to the study. This increase would take place through the functional LINKs that could be re-activated by the extra-hippocampal circuitry. Thus, the amount of pre-operative experience determines whether memories become partially or completely independent of the hippocampus at remote time points [38].

It was reported that as memories are transferred to the cortex, memories stored in the hippocampus are reduced [55]. The semblances formed through the newly formed functional LINKs at the hippocampus immediately after learning contributes to the retrieved memories immediately following learning. The new neurons integrated into the circuitry may cause reduction in specificity of the semblances formed from the hippocampus if no repetition of learning, or reactivation of receptor pairs or retrieval of memories takes place. However, integration of new neurons along with repetition of learning or reactivation of receptor pairs or retrieval of memories shifts the origins of required semblances towards the cortex and support the findings that hippocampus is not required for the precision of remote context memories [56].

Discussion

The present work has sought a feasible synaptic mechanism that can possibly explain the transfer of memories from the hippocampus to the cortex using newly formed hippocampal neurons. This was possible only by viewing memory as a virtual sensation of sensory stimuli formed from the integration of the synaptic and network semblances. The idea of semblance formation is supported by arguments that suggest a lack of content for stored memories [57]. The spread of EPSPs within an islet of LINKed post-

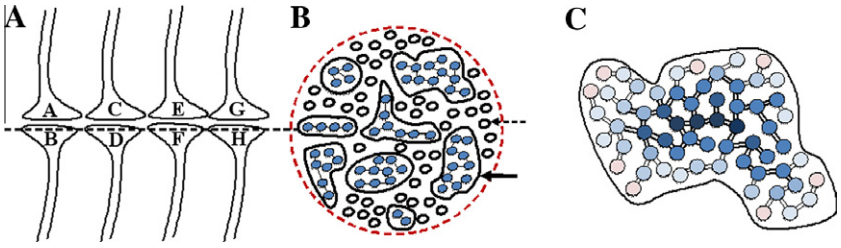

Fig. 6. Islets of functionally LINKed postsynapses and their contribution to the stability of memory. (A) Four synapses are shown side by side that have the potential to form functional LINKs between their postsynapses (dendritic spines). The dotted line shows cross-section of all the postsynapses. (B) Hypothetical cross-sectional view through a large number of postsynapses as shown in the left panel. In this illustration, the cut surfaces of the postsynaptic membranes are assumed to be in the same plane. When learning occurs, functional LINKs are formed between the simultaneously activated postsynapses. Continued learning using any of those already LINKed postsynapses will increase the number of inter-LINKed postsynaptic membranes forming islets of functionally LINKed postsynapses (solid arrow). The individual islets are expected to be functionally separate from each other. (C) Schematic representation of one islet of functionally LINKed postsynapses. Rarely used LINKed postsynapses (pink circles) move towards the periphery in a large islet of functionally LINKed postsynapses as commonly used ones (dark blue) move towards the center of an islet (the periphery-central movement need not be limited to a structural event; functional aspect of the LINKs should also be considered). Newly LINKed postsynapses (pink) remain at the periphery of an islet. The rarely used and newly formed functional LINKs will lose their function quickly unless re-used. Even though islets are considered functional in nature, those postsynapses at the center (dark blue) may eventually develop more stable functional LINKs. Note that the locations of the positions of the postsynaptic terminals in the graphic of the islet are not to be scaled since they need to be visualized as functional LINKs in a functional space. (figure was used after modification [39]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

synapses offers degeneracy qualities for the representations of memory. The advantage of this property is likely to come with a cost. Since the islet of functional LINKs (Fig. 6) expands in size due to additional learning events, the net semblance formed from the re-activation of functional LINKs in the hippocampus alone will reduce the specificity for memory retrieval as time advances after new learning. This is due to the dilutional effect of non-specific semblances formed due to the spread of EPSPs in the islet of functionally LINKed postsynapses. However, as different associative learning events with similar cues occur (indicated by an increase in size of the islets of functional LINKs), a highly specific cue will be required for specific memory retrieval. This may explain why gist memories increase as related learning increases [58], providing an increase in sensitivity for memory retrieval, probably at the cost of specificity.

New neuron-induced formation of additional functional LINKs in the cortex which induces net semblance for a particular memory can reach a plateau, indicating that learning beyond certain limits won't provide any added retrieval benefits. It also supports the idea that the qualities of retrieved memories do not change after improving the specificities of the cue beyond a certain limit. The locations in the cortex where semblances are formed move farther apart as the sensory inputs reach higher orders. It may be possible that the overlap between semblances originating from widely separated synapses (Fig. 1d) in the cortex may bring more specificity to the net functional semblance and may support the findings that the hippocampus is not required for the precision of remote context memories [56].

Synaptic and systems consolidation

It has been suggested that there are two different types of time-dependent memory stabilization processes, namely synaptic consolidation that lasts hours and systems consolidation that lasts years [29]. Based on the present work, an explanation for both can be made as follows. The newly formed functional LINKs first remain at the periphery of an islet of functionally LINKed postsynaptic membranes (Fig. 6). Alternations in the shape of dendritic spines have been viewed as an enduring property of the nervous system [59]. Moving the functionally LINKed postsynapses towards the center of an islet makes their residence within the islet more stable. This is achieved by the use of functional LINKs through: (1) repetition of learning, (2) related learning, and (3) unrelated learning either by activating the receptor pairs or activating the functional LINKs used during the original learning event (without activity from the sensory receptors).

Re-activation of the functional LINKs for a long period of time and stabilization of the functional LINKs through activation of biochemical mechanisms (for example, by dopamine in motivation-induced learning), may convert these LINKs to more stable near-structural LINKs [39]. This process can be seen as equivalent to synaptic consolidation. The transfer of memories through an increase in semblances in the cortex that is described in the present work, during consolidation, can be viewed as systems consolidation. Reactivation of hippocampal ensembles [60] and neuronal oscillations occurring during sleep [61] may also re-activate the functional LINKs formed during learning and increase their re-activability properties.

Storage versus retrieval defect in amnesia

It has been found that shortly after learning or the retrieval of learned items, stored memories can be impaired by electroconvulsive shock (ECS) [62,63] or by competing new learning processes [64,65]. Different studies have resulted in different views about the nature of the amnesia induced by the above protocols. These include reversible or irreversible amnesias that are either storage-defective or retrieval-impaired [66]. Questions have also been raised about whether all cases of amnesia need to be either storage or retrieval defective [67]. There have also been suggestions that amnesia is only a graded process and that residual traces remain [68]. Based on the present work, these different findings may be explained as follows. The retrieved memories, which consist of net semblances that are internal properties of the nervous system, are studied through behavioral changes observed in animals. Concurrent with the formation of the functional semblance, a partial

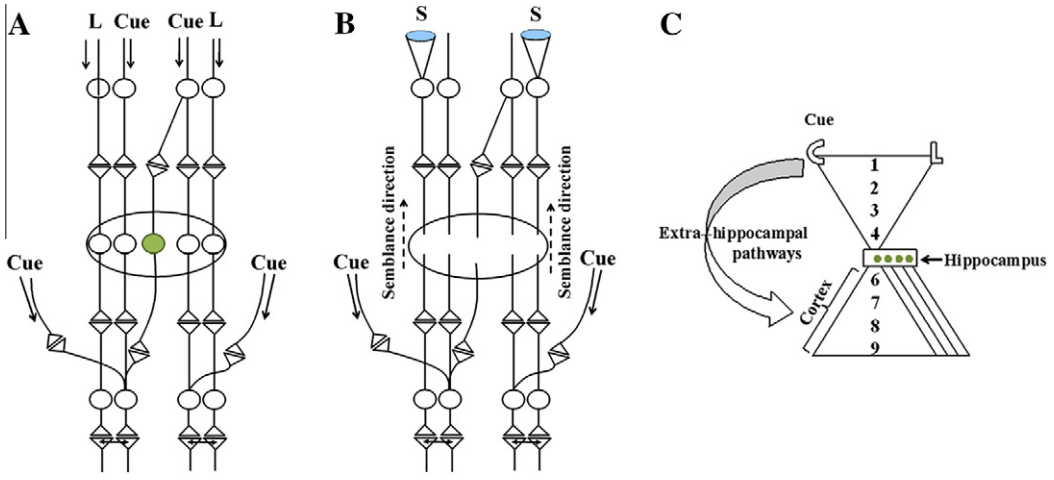

Fig. 7. Transfer of representation of memory from the hippocampus to the cortex. It is the build-up of excess functional LINKs in the cortex that enables the cortex alone to induce sufficient semblance for memory retrieval. (A) Large elliptical shape represents the hippocampus. Small circles with it are the granule neurons. Green circle among them is a new granule neuron. One new hippocampal neuron is incorporated into the circuit that enables an additional functional LINK formation (marked by an asterisk) provided the receptor pairs that were used during the initial learning are re-activated after the new neuron has made input and output synaptic connections. The formation of an increased number of functional LINKs takes place in the cortex over time due to the repetition of learning, the learning of related items and the retrieval of memories. (B) Empty elliptical shape represents the loss of hippocampi. Cue stimulus, by activating the extra-hippocampal pathways, induces semblance for the learned item. There is no requirement for the physical presence of the neuronal pathways from the postsynapse where semblance is elicited to the sensory receptors from which it likely get sensory inputs. (C) A summary diagram representing an increase in the number of functional LINKs in the cortical regions, through the integration of hippocampal new neurons, from where semblances form during memory retrieval by activation through extra-hippocampal pathways. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

network of neurons (Fig. 1d) is activated that can directly or indirectly activate behavioral motor circuitry. ECS may destabilize the functional LINKs, preventing their re-activation.

Since completely new learning can share some of the sensory receptors used in the previous learning, it leads to the induction of new functional LINKs with the postsynapses that have already formed functional LINKs with other postsynapses during previous learning events. During memory retrieval using a specific cue, the number of net semblances elicited through the functional LINKs within an islet increases and becomes diluted due to the integration of non-specific semblances. This dilution effect on semblances provides a novel reason for amnesia distinct from storage or retrieval defects [66]. Amnesia can only be complete if all the functional LINKs formed during a specific learning event are destroyed. Since most learning involves sensory receptor pairs and their preformed functional LINKs, it is not theoretically possible to create an absolute state of amnesia for any learning event.

Other effects of new neurons

As hippocampal neurogenesis changes the locations of stored memories, it can also have unfavorable effects on specific memory storage, if there is neither repetition of learning of the original or related items, activation of receptor pairs used in the original learning event by other learning events, nor the re-activation of the functional LINKs induced by original learning event. After one learning event, new neurons that become incorporated in its circuitry will cause retrieval of memories to induce non-specific semblances that were not specifically associatively learned for that particular item, provided there were no activations of the receptor pairs used in the earlier learning event (Fig. 3). These non-specific semblances will dilute the semblance from specific functional LINKs formed by the original learning event. This is supported by the suggestion that new granule neurons integrated into the hippocampal circuitry can degrade existing memories [69]. Even though one learning event that shares a subset of receptor pairs with a previous learning event improves the efficiency for specific learning, it might also lead to reductions in specificity during memory retrieval.

Conclusion

By viewing memory as a virtual sensation of a sensory stimulus that remains as an internal property of the nervous system, it is possible to hypothesize how memories may get transferred from the hippocampus to the cortex during the consolidation process. New neuron-induced formation of additional functional LINKs in the cortex can provide excessive semblances from the cortex, evoking the effect of an apparent transfer of memories from the hippocampus to the cortex. The nature of the retrieved memories results from the integration of semblances and depends on the specificity of the cue stimulus. Even though nervous system does not possess a computational system, the net semblances from different locations are naturally computed to form the net semblance. Due to synaptic delay, time is a dimension used in those computations. The presence of pre-existing functional LINKs that can be used in a transferable way is an important quality used for quick systems consolidation of memories if an associative schema has previously been created into which new information is incorporated [53]. Formation and deletion of synapses and genetic and environmental factors can bring minor variations to the net semblances. As this hypothesis provides a suitable framework for the transfer of memories, searching for the characteristic properties of the functional LINKs may enable us to decipher the specific features of the basic units of memory storage. The present hypothesis should be treated as unproven until it is verified against further experimental evidence.

Conflict of interest

There are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work "A possible mechanism of transfer of memories from the hippocampus to the cortex".

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