J. Indian Inst. Sci.
A Multidisciplinary Reviews Journal
ISSN: 0970-4140 Coden-JIISAD

REVIEW ARTICLE

Neural Circuits of Memory Consolidation and Generalisation

P. Meenakshi[*] *and J. Balaji*[*]

Abstract | Memories of lifetime experiences, events and facts are thought to be acquired through part of the brain region termed hippocampus. These memories are very distinct when they form initially. However, in due course of time after their formation, these memories become less specific. This process of losing specificity and being able retrieve a memory at the presentation of cues that are related, though not necessarily the same as the one that was initially used, is termed generalisation. In this review, first we propose a modification to the categorisation of memories based on lifetime of memories and then proceed forward to introduce the idea of memory consolidation at various scales and their relevance to generalisation. We conclude by reviewing some of the recent pertinent methodologies and their basis in performing these studies.

Keywords: *Remote memories, systems consolidation, generalisation*

1 Introduction

The fascination to understand our ability to acquire, retain and remember information drove Hermann Ebbinghaus, a German psychologist, to study the phenomenon of memory through introspection. Despite its severe limitations, this first attempt to understand memory processes revealed quite a few interesting aspects of memory, such as how memory strength is dependent on the number of repetitions and prior knowledge. Since then, our understanding of how memories are formed, consolidated and retrieved has advanced significantly. In parallel, many new methods, animal models and tools have been developed to study these processes. A broader and more general picture of how the memories are organised and stored emerged from these studies, particularly from those involving amnesic patients[1] and animal lesion[2] experiments. In general, these studies have led to the picture that memory is not a unitary process and it has many categories, with each one of them having a locus in the brain; thus, leading to the classification of the memory system to its subtypes based on neuroanatomical as well as functional differences. Memories of events, facts, space and autobiographical memories are all thought to be dependent on the hippocampus, at least for the initial formation of these memories. The defining characteristic of these memories is the ability to retrieve and recall these events in a conscious manner at one's own will. These hippocampal-dependent memories that can be retrieved consciously are termed as declarative memory as against memories that do not proceed through conscious recollection (non-declarative). For example, when you try to recollect the colour of your bicycle (fact) or when you rode it last (event) and/or where it is parked (place), you are exercising your declarative memory, but the moment you get onto the bike it is the unconscious recall of how to pedal while keeping the balance that lets you ride it (procedural memory). Declarative memories are shown to be strongly dependent on the hippocampal sub-region of the mammalian brain for their initial formation. Lesioning the hippocampus results in a clear deficit of its ability to encode and store new events as well as facts[3]. However, the retrograde amnesia that results from such lesions is temporally graded. The memories of events that occurred closer in time to the lesion are more prone to loss, while

P. Meenakshi and J. Balaji have contributed equally to this article.
Center for Neuroscience, Indian Institute of Science, 560012 Bangalore, India.
**meenakship@iisc.ac.in; jbalaji@iisc.ac.in*

Springer IISc Press

memories that are much older are resistant to the loss. This is very much in accordance with Ribot's law[4]. Theodule Ribot observed that retrograde amnesia seen in patients following a disruptive event is temporally graded such that it preferentially loses the memories of events that occurred closer to the disruption. The evidence for this law came in the form of studies from patients undergoing electroconvulsive therapy (ECT)[5] and amnesic patients such as HM[1]. Apart from providing insights into how such a temporal gradient can be maintained, these studies when extended to animal models paved the way for understanding the finer inner workings of the memory process itself.

1.1 Consolidation at Multiple Scales

Memories during the period immediately after acquisition are susceptible to changes through interference, facilitation and many other processes. While the time window is dependent on the type of memory, in general this time window is thought to be about a few hours. However, they become more resistant to these changes as the time progresses. This process of initially susceptible memory becoming resilient over time is termed as consolidation of memory.

1.1.1 Phases of Memory

Ebbinghaus, based on his studies, predicted that there ought to be different classes of memory depending on the lifetime of memory retention. In his word list experiment, he plotted the percentage of words that he could retain as a function of time delay between the training and retrieval. The resulting curve (Fig. 1a), famously known as "the forgetting curve", showed that his ability to remember varied widely. Based on this, he argued that there must be different phases of memory. These phases are now more formally defined using theoretical and experimental observations. From a behavioural perspective, the memory per se can be thought of as consisting of the following steps: (1) acquisition phase—the initial phase where the memory is getting formed and is more prone to interference, modulation and disturbance; (2) consolidation phase—the phase after which the memory is strengthened and becomes resilient; (3) retrieval—this is the phase where the strength of the memory is tested for its expression through the presentation of cues; (4) extinction/reinforcement—the phase where the expression of the memory is modulated post-consolidation (Fig. 2).

Another convenient classification of the memory processes is based purely on the transiency of the memory. The transiency of the memory is defined in terms of how long after the formation can the memory be retrieved. In this review, we would like to make a distinction between two kinds of phases, one that is defined by the retention ability without an explicit test on retrieval (working memory) and the other where the transience is tested through explicit retrieval. The first arises due to information retention ability and the latter requires the ability to retrieve and express the memory after a delay. The former is defined as the working memory (ref: Miller 1956 and Miller et al. 1960). It refers to one's ability to retain the information until the duration of the task. In this review, we associate the second category where the retrieval process is explicit as the "sustenance phase" of the memory. This phase can again be subdivided further as described below.

Memories as they form can be retrieved in a seemingly continuous manner even during the initial periods where it is susceptible to modification. Clearly for memories to be retrieved after a time gap, they need to have a supporting representation throughout the time. Given that permanent memory forms slowly and there must be a possibility for estimating the contingencies across many trials, it has been suggested that there exist many parallel processes that can support the retrieval of the memory during this phase. These processes are postulated to last until the consolidated memory is fully formed, thus leading to the suggestion that memories have multiple phases and are supported by parallel processes that are temporary [6].

1.1.2 Cellular Consolidation

Based on the experimental evidences involving pharmacological interventions and explicit retrieval process detailed below, it is reasonable to assume the existence of the proposed "sustenance phase" for the memory process. This process is further classified into three different temporal stages of memory, viz., (1) immediate memory (minutes to hours), (2) short-term memory (< 24 h) and (3) long-term memory (> 24 h). These time-dependent processes are shown to be governed/controlled by different molecules. For example, using antibiotics as protein synthesis inhibitors, it has been shown that de novo protein synthesis is required for encoding/forming memory in general. Transcranial infusion of the antibiotic puromycin during a shock avoidance task

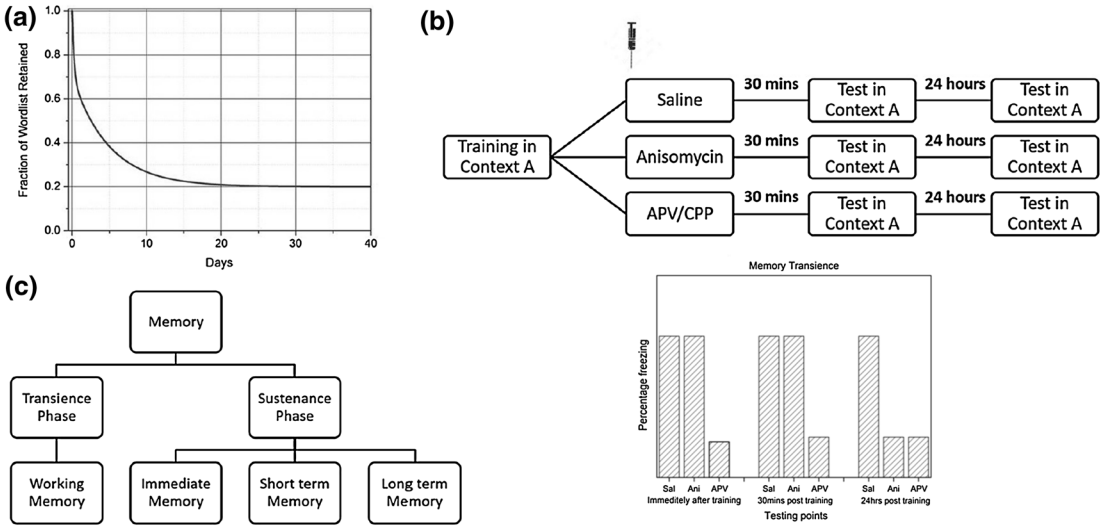

Figure 1: Phases of memory: **a** Ebbinghaus forgetting curve. The solid line represents the famous "forgetting curve". The curve illustrates the fact that most of the memory is lost in the initial few days and ~ 20% is retained for a long time. From this, Ebbinghaus proposed existence of (1) immediate-term, (2) short-term and (3) long-term memory. **b** Cellular consolidation. Defining the different phases of memory through molecular manipulations. Infusion of drugs at different intervals after training helps define different phases of memory. In this hypothetical experimental schematic, the animals trained in a behavioural task (preferably one-shot learning) are divided into three groups. (1) Saline group, (2) anisomycin group and (3) APV/CPP group. The bar graph illustrates the expected behavioural outcome after infusion of anisomycin (protein synthesis inhibitor), infusion of NMDAR blocker (APV/CPP) and saline. The memory when tested immediately was expressed in all three cases. However, the anisomycin group expresses memory only in 30 min testing group, but not in the 24 h testing group. **c** The memories can be classified based on the time of persistence. The memories that are required and used when performing a task (working memory) and memories that come into play during a retrieval act.

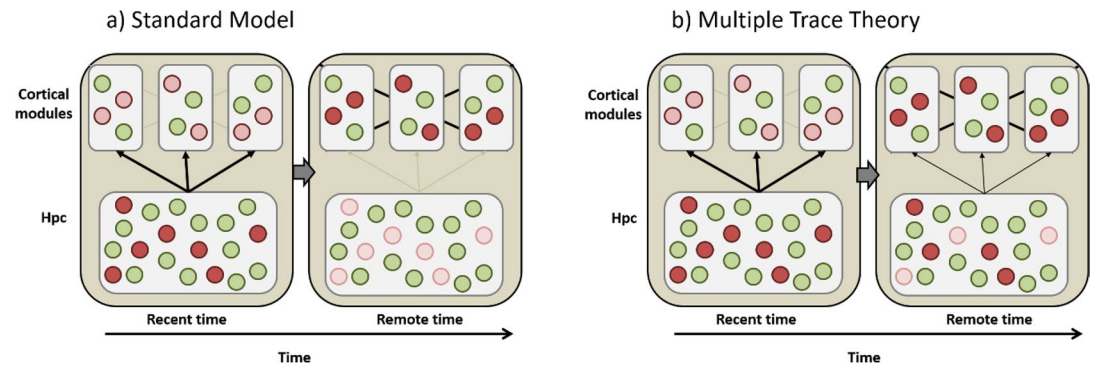

Figure 2: Schematic representation of the models for systems consolidation. Red circles represent the neurons that were activated during retrieval of the memory. At the recent time point, the hippocampus is the predominant player in memory expression. However, the neurons in the cortical modules also have a role to play in remote memory expression. **a** Standard model of systems consolidation: the activated neurons in the cortex (red circles) are the ones involved in the remote memory expression, which is now completely independent of the hippocampus (white circles). **b** The activated neurons in the cortex as well as the hippocampus (red circles) are required for the detailed expression of the memory at a remote time point.

in goldfish impairs the formation of associative memory. In these experiments where memory impairment is measured as function of time delay between training and administration of puromycin, it is seen that the effect of drug diminishes with time[7]. This suggests that memory consolidation (formation of memory that is nearly resilient to modifications) is a time-dependent process and once the memory is consolidated then it becomes resistant to such changes.

In addition, experiments using mice in water maze as well as contextual fear conditioning experiments reveal that infusion of NMDAR receptor blockers during training impairs the acquisition without affecting the animal's performance in the task[8].

1.2 Systems Consolidation

Consolidation of memory in general refers to a transition wherein the original memory that is susceptible to disturbance becomes more resilient in due course of time. True to that principle, systems consolidation of declarative memory takes place over longer timescales (weeks to months in rodents and months to years in humans), wherein the memory becomes resilient to lesioning of the hippocampus. During this process, the memories of events and facts, which were once dependant on the hippocampus for its retrieval, become independent of the hippocampus. Evidence for this arises from studying patients with hippocampal damage such as H.M and A.P. The patient H.M had his medial temporal lobe (hippocampal and parahippocampal regions) removed to manage intractable epilepsy. As a result, he was unable to remember any new event after the surgery. However, his older memories, such as his childhood memories, were intact and any loss in these memories was similar in magnitude to that of normal humans. This suggests that though the hippocampus is needed to form new declarative memories, with passage of time they can be retrieved independent of the hippocampus.

In one of the interesting studies to test the nature of the memory that is lost during the medial temporal lobe lesions, the patients who were amnesic for the episodic memory were trained on serial reaction time task. This task is designed such that the subjects can be probed for how well they have mastered a given sequence that is presented in an implicit manner (the subjects are not informed if the objects are displayed in any order). Their performance can be followed by measuring their reaction time/response time, while the episodic or declarative nature of the memory can be probed through a list of questions. These studies when done in amnesic patients[9] showed that though they were not aware of the task (no declarative memory of having been trained in the task), their reaction time in a serial reaction time task kept improving (kept reducing). They were learning and their performance was getting better; however, they did not know that they were engaged in any such learning. This is despite the fact that participants were completely unaware if there was any meaningful order that was being implicitly presented. Thus, the study showed for the first time that the skill/procedural learning can occur without the conscious knowledge of the persons who are engaged in such tasks.

Human studies involving amnesic patients helped in advancing the field in a considerable manner. Simultaneous development of animal models was difficult to come by, since the equivalence of conscious recollection in rodents and other lower-order mammals are hard to establish. However, identification of behavioural tasks that is dependent on the hippocampus paved the way for arriving at the aspects of declarative memory that can be trained and tested in animal models. In rodents, the graded nature by which the memory becomes independent of the hippocampus was shown by Kim and Fanselow[2]. In these experiments, groups of mice underwent contextual fear conditioning (CFC) training to associate a shock (US) with a context A (CS). The experiment was done with a slightly larger group of animals to start with, and a smaller subgroup of animals had their hippocampus lesioned out at different delays after the training. It was observed that hippocampal lesions at different time points caused graded retrograde amnesia. Animals that underwent hippocampal lesions after 28 days showed memory retrieval comparable to the control animals, indicating that these memories have become resilient to hippocampal lesions and can be retrieved independent of the hippocampus. Thus, this whole process is termed consolidation at the systems level or systems consolidation in short. These systems consolidated memories are the memories of events that occurred some time back or at a remote time point and they are termed remote memory.

1.2.1 Box 1: Behavioural Paradigms for Studying Memory in Rodents

1.2.1.1 Contextual Fear Conditioning Contextual fear conditioning (CFC) is a multimodal memory task. During training, mice are taught to associate a con-

text (CS, training context A) with a foot shock (US). Memory retention of this association is tested by bringing the mice again into the same context and measuring its freezing response (CR). The freezing response in rodents is an evolutionary response to a stressful situation, which can be defined as cessation of all movements except for breathing. The memory for the context has been thought to be stored in the CA1 region of the rodent hippocampus.

Context-dependent memory in rodents is episodic-like memory, since both context-dependent memory in rodents and episodic memory in humans consist of representations of a detailed spatio-temporal context which depends on the hippocampus.

1.2.1.2 Water Maze During the time, the scientific world serendipitously discovered the role of hippocampus in declarative memories in H.M., followed by many such patient studies. R.G. Morris devised a new behavioural paradigm to integrate the aspects of memory as well as space. The Morris water maze is a paradigm where the rodent is placed in a circular enclosure filled with water with a hidden platform located in one of its quadrants. It exploits the fact that rodents are good swimmers but dislike water. Hence, they are motivated to find the hidden platform that allows them to escape from the water. The location of the platform can be learnt with respect to the visual cues present on the walls of the room containing the maze. After training the rodents to learn the location of the platform, their memory for its location is tested in a probe trial where the platform is removed and the resident time of the mouse in each quadrant is measured as a proxy for memory recall.

Since then, many variations of the Morris water maze were used to study spatial memory, such as the radial arm maze or delayed matching to place task. Barnes' maze is another variation which is a dry maze version to reduce the stress associated with placing rodents in a water environment.

1.2.1.3 Social Transfer of Food Preference Social Transfer of Food Preference is a memory retention test used in rodents based on olfactory cues. When presented with a novel food flavour, an evolutionary survival instinct drives the rodent to eat the food previously consumed by its conspecifics. The paradigm allows for the interaction between an observer mouse with a demonstrator mouse that has consumed a specific novel flavour. During the interaction, the observer mouse detects the odour of the novel food consumed by the demonstrator mouse and forms an olfactory memory for the same. Then, the observer mouse is presented with the two novel flavours, one of which was previously consumed by the demonstrator mouse. Based on the amount of consumption of the novel flavour food which was previously eaten by the demonstrator mouse, we can measure the olfactory memory retention in the observer mouse. Thus, it can be used for studying remote nonspatial memory[10].

1.2.1.4 Novel object recognition Novel object recognition (NOR) task was first used by Ennaceur and Delacour[11] and exploits a rodent's innate exploratory behaviour. The test involves placing novel as well as familiar objects in an environment for the rodents to explore. Inherently, rodents prefer to explore novel objects more than familiar objects given in an environment. The exploration time or residence time with the different objects can be used as a measure for memory. It can also be used to study whether an animal is able to discriminate between novel and familiar objects. This task does not rely on any association/reinforcement/rule learning as compared to other behavioural paradigms such as CFC.

1.2.2 Standard Model for Consolidation

Putting together the results, observations and inferences from a variety of studies involving amnesic patients and lesion studies on animals and several other aspects, Alvarez and Squire put forward a generalized picture of how our memory system functions. The model presents us with a 'standard' to relate, compare and understand many aspects of the memory processes. It is popularly referred to as the standard model for memory consolidation in the field. The standard model for consolidation[6] states that memories become independent of the hippocampus through repeated reactivation of the hippocampal–cortical connections, either through cue-mediated recall or by reactivation of the memory during sleep or through active replay (imagination). Such a reactivation leads to strengthening of connections between the distributed cortical networks that originally were integrating the sensory input in the first place. Such a strengthening among the cortical modules is probably mediated through the pre-frontal cortex. It is thought that eventually when SC is complete and the cortical encoding can support the retrieval, the memories are thought to become independent of the hippocampus thus explaining the observations made in the amnesic patients or in lesion studies. According to standard model of systems consolidation , at this point the memory exists in the

Systems consolidation: The process through which the memory once formed in hippocampus(a region of mammalianmamalian brain) acquires the ability to be retrieved independent of hippocampus.

extra-hippocampal regions and is fully capable of supporting cue-mediated retrieval independent of the hippocampus. While in the absence of the hippocampus the memories can be supported by the cortical representation, the role of an intact hippocampus during the remote retrieval if any is very intensely debated. One of the prominent alternate views is that hippocampal trace as well as cortical trace exists simultaneously.

1.2.3 Multiple Trace Theory

An alternate model to explain systems consolidation is the multiple trace theory (MTT). MTT hypothesise that the hippocampus plays a role in episodic, but not semantic, remote memory, i.e. contextual memory is always dependent on the hippocampus for details, whereas semantic memories are independent of hippocampus after systems consolidation.

1.2.4 Role of Cortical–Hippocampal Circuits at Recent and Remote Time Points

Evidence for remote memory dependence on the hippocampus comes from optogenetic studies, where inhibition of the hippocampus immediately before testing remote memory retrieval affects the memory[12], and hippocampal inactivation impairs the expression of specific but not generalised memories[13].

Lesburgueres et al.[14] showed that inhibition of the cortical circuit within 24 h after memory acquisition affected the ability of the animal to retrieve the memory at remote time points, thus indicating the role of the hippocampal–cortical circuit, and not just the role of the hippocampus, at the recent time point in retrieval of remote memories.

In this review, we maintain that the formation of cortical representation is a continuous process that proceeds slowly. Thus, the relevance of the hippocampal trace diminishes slowly, though not entirely. In addition, we also subscribe to the notion that there would be hippocampal as well as cortical memory traces formed simultaneously at different rates, with cortical rate much slower than the hippocampal rate[15]. Thus, it takes more number of trials for a given associative pair to be encoded in the cortex as compared to the *hippocampus.*

Optogenetics: Methodology that utilises probes/ channels or reporters that can be driven through gene expression and activated/probed through optical means.

1.3 Memory Trace or Engram

Memory trace or engram is an ensemble of neurons which might constitute the physical representation of a memory. This concept was proposed by Richard Semon in 1921 as the Engram Theory[16]. Learning-induced activation of a small ensemble of neurons results in persistent changes on the neuron that stores the information. Reactivation of this ensemble by relevant recall cues results in retrieval of the specific memory.

1.3.1 Immediate Early Genes in Plasticity

Synaptic signals received by the neuron need to be translated into long-term plasticity in the neuronal circuit. Immediate early genes or IEG are rapidly expressed following neuronal stimulation. Its expression is tightly correlated with synaptic plasticity. The function of IEGs ranges from acting as growth factors, structural proteins, signal transduction molecules to being transcription factors that affect gene expression. It has a supposed role in stabilising recent changes in the synaptic efficacy[17].

IEGs are used as activity markers for mapping neuronal circuits activated during various behaviour paradigms. It provides a tool to determine the involvement of various brain regions in encoding a behaviour. The specificity of the expression for a given memory becomes difficult, as stress and arousal also lead to its expression. However, with the ability of in vivo imaging and by maintaining a controlled environment, we can overcome this problem as it allows us to look into the same animal at different time points.

1.3.2 Evidences for Memory Engram/Trace

The advancement in molecular tools now allows us to label or tag the neurons that were activated during learning. One study showed that the same neurons that were activated by exposure to a novel context in the CA1 of the hippocampus were reactivated when re-exposed to the same environment[18]. Another study employed transgenic mice to enable differential tagging of distinct populations of activated neurons. Mice trained in fear conditioning showed that the same neurons in the amygdala that were activated during learning were also activated during recall[19].

Development of optogenetics tools, which allow to manipulate the activity of neurons, further verified that reactivation of tagged cells manifested in the expression of a specific memory. When hippocampal neurons activated during context fear conditioning were reactivated in a novel context, the animals showed freezing response to a context it was never exposed to before[20,21]. A similar experiment was done in the retrosplenial cortex

(RSC) where reactivation of the neuronal ensemble was sufficient to induce a fear response[22].

1.3.3 Box 2: Examples of IEGs

Immediate early genes are a group of genes that are expressed rapidly in response to a variety of cellular signals including growth factors, tumour progression, cell stimulation, etc. These genes were first identified when cells were exposed to mitogens. Their role has been implicated in a wide variety of cellular processes including cell growth, cell cycle regulation and cell maintenance. Here, we focus on how IEGs are rapidly expressed following neuronal stimulation and their expression being tightly correlated with synaptic plasticity.

IEGs are classified into affectors and effectors. Affectors are genes upstream of the signalling cascade, mainly transcription factors that alter the transcriptome on receiving the cell signal, for example, cFos, c-jun and zif-268. Effectors are genes that directly alter the plasticity such as cytoskeletal proteins (activity-regulated cytoskeleton-associated protein, Arc), scaffold proteins (Homer) or growth factors (brain-derived neurotrophic factor, BDNF). A few of these are briefly described below.

1.3.3.1 IEG: Arc Activity-regulated cytoskeleton-associated protein (Arc) is a structural protein that is localised to the dendrites. Disruption of Arc impairs the maintenance phase of LTP and consolidation of long-term spatial memory[18]. The kinetics of Arc mRNA are such that a few minutes after activation, it is localised in the nucleus as intense foci, while 30 min later it is accumulated in the cytoplasm and dendrites of the cell[18].

1.3.3.2 IEG: cFos cFos was one of the first IEGs to be identified. It was previously identified as a proto oncogene, which suggests its regulatory role in the cell cycle[23].

The first demonstration of cFos expression in vivo was shown in response to pentylenetetrazol (PTZ), a gamma-aminobutyric acid (GABA) antagonist that causes seizures in mice. Seizures produced widespread cFos expression throughout the hippocampus, basal forebrain and cortex with mRNA levels peaking 60 min and protein levels peaking 90 min following seizure induction.

Normal forms of cell stimulation such as visual sensory stimulus and whisker stimulation induced cFos expression in the suprachiasmatic nucleus and the somatosensory cortex, respectively. In mice, contextual fear conditioning induced peak levels of Fos protein in regions throughout the brain 60–90 min following learning.

A conditional cFos knockout mouse line, limited to the hippocampus, showed normal spatial memory expression only when trained using an intense protocol for water maze. Another knockout mouse line lacking cFos in both neurons and glia showed spatial memory deficits using a less intense training protocol in the water maze (one trial per day for 11 days) and also showed deficits in long-term memory for contextual fear conditioning. Disruption of cFos function using antisense oligonucleotides in the hippocampus also resulted in impaired spatial memory in the water maze. It had no effect on short-term spatial memory, but did affect long-term memory.

The above suggests that cFos may play a general role in coupling stimulation to long-term changes in gene transcription required for plasticity changes in the neuron.

1.4 Generalisation

The process of memory consolidation is susceptible to change. Generalisation of a memory refers to the loss of details in specific memory over time. Since it is thought that memories once having undergone system consolidation takes representation in the cortical areas, the possible mechanism by which systems consolidation takes place manifests in the expression of a generalised memory. The standard theory views memories as transferred from the hippocampus to a stabilised cortical representation over time, allowing the hippocampus to encode new memories, whereas the multiple trace theory emphasises the dynamic nature of a consolidated memory as detailed hippocampal representations co-exist with generalised cortical representations. The standard theory maintains that detailed episodic memories can become independent of the hippocampus over time, whereas the multiple trace theory emphasise the distinction between two types of declarative memory, episodic and semantic, proposing that detailed episodic memory always requires the hippocampus for expression. All the evidences point to the fact that the nature of memories encoded by the distributed cortical trace or the hippocampal trace is different at a remote time point compared to the recent time. Little is known about the circuit level changes/neural correlates of memory. However, behavioural tests in rodents have shed light on the nature/characteristics of generalisation of memories.

Generalisation: Ability of related cues to retrieve the memory / elicit a behavioral response that is associated with a previous experience.

1.4.1 Behavioural Data in Animal Models Showing Generalisation

In rodents, animals trained to associate context A (CS) with a foot shock (US) can clearly distinguish the training context A with a novel context B that is similar (closely resembles context A) during memory retrieval 24 h later. However, if the animal is tested for memory recall at a remote time point, it tends to show freezing in both the training context A and a novel context B, i.e., the fear memory gets generalised to both contexts over time.

In a study by Richards et al.[24], mice were trained in modified water maze paradigm where the platform was randomly placed around the mean of a spatial distribution, but never at the mean. During the probe trial, one-day post-training, the mice could recall where the platform was last placed during training (measured by time spent in the area). However, 30 days post-training, the mice recalled a generalised memory of where the platform was placed. They spent majority of the time at the mean of the platform distribution, which was one of the positions where the platform did not appear during training.

In a related study using discrimination training, the animals were trained to associate context A (CS) with a foot shock (US) (shock context) as well as learn to associate context B with the absence of foot shock (safety context). The sensory features of the context can be modified such that the two contexts have some similar overlapping features. Yet, these animals that undergo discrimination training can clearly distinguish between context A as the shock context and context B as a safety context, even during memory retrieval at a remote time point even after hippocampal lesions. This suggests that cortical memory can also be detailed under such circumstances.

1.5 Conclusion and Future Directions

Little is known about the mechanisms that are operating when the memory gets generalised because of the systems consolidation process. This is especially true if we want to understand the processes at the level of neuronal circuits. As discussed in the review, despite a large body of work done to establish and understand systems consolidation, our understanding about how and why memories change during this process is very limited.

As we have mentioned earlier, Ribot's law states that more recent memories are prone to disruption in comparison to older memories. One of the possible mechanisms by which this behavioural readout manifests is if each time an event is experienced, the neuronal circuits corresponding to the congruent details are reactivated and strengthened compared to the neuronal circuit of the uncommon elements of that event. Thus, as the memory becomes older, it is possible that the congruent details are consolidated more frequently and hence at a faster rate in the cortical structures. On the other hand, the unique details that define the specificity do not get strengthened. Such selective strengthening of common details across multiple related events would cause the memory to become generalised. This ensures that the older memories whose trace is now in the cortical structures is more resilient to disruption. The neuronal and circuit level mechanisms that may possibly underlie such transitions (as that of the memories of closely related or similar events losing its specificity and getting generalised over time) are not well understood. For example, it is not known whether the inputs received at the cortex is itself sparse or encoding of the memory in the cortex becomes sparse during systems consolidation.

One of the limiting factors in the studies involving multiple memories is the lack of the ability to identify and follow specific neuronal ensembles that might encode similar memories during systems consolidation. Apart from cellular identities of a neuronal ensemble encoding different memories, the functional connectivity between the different neuronal ensembles could evolve to represent or provide generalisation across multiple memories. Thus, one of the key objectives in the field is the development of such methods at the neuronal level and address how the generalisation comes about through the process of systems consolidation.

Received: 22 September 2017 Accepted: 24 October 2017
Published online: 11 December 2017

References

1. Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neuropsychiatry Clin Neurosci 20:11–21
2. Kim JJ, Fanselow MS (1992) Modality-specific retrograde amnesia of fear. Science 256:675–677
3. Squire LR, Alvarez P (1995) Retrograde amnesia and memory consolidation : a neurobiological perspective. Curr Opin Neurobiol 5(2):169–177

4. Ribot T (1882) Diseases of memory: an essay in the positive psychology. Science. https://doi.org/10.1017/CBO9781107415324.004
5. Squire LR, Slater PC, Chace PM (1975) Retrograde amnesia: temporal gradient in very long term memory following electroconvulsive therapy. Science 187:77–79
6. McGaugh JL (2000) Memory—a century of consolidation. Science 287:248–251
7. Agranoff BW, Klinger PD (1964) Puromycin effect on memory fixation in the goldfish. Science 146:952–953
8. Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG (1995) Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. Nature 378:182–186
9. Reber PJ, Squire LR (1994) Parallel brain systems for learning with and without awareness. Learn Mem 1:217–229
10. Singh A, Kumar S, Singh VP, Das A, Balaji J (2017) Flavor dependent retention of remote food preference memory. Front Behav Neurosci 11:7
11. Ennaceur A, Delacour J (1988) A new one-trial test for neurobio-logical studies of memory in rats. Behav Brain Res 31:47–59
12. Goshen I, Brodsky M, Prakash R, Wallace J, Gradinaru V, Ramakrishnan C, Deisseroth K (2011) Dynamics of retrieval strategies for remote memories. Cell 147:678–689
13. Wiltgen BJ, Zhou M, Cai Y, Balaji J, Karlsson MG, Parivash SN, Li W, Silva AJ (2010) The hippocampus plays a selective role in the retrieval of detailed contextual memories. Curr Biol 20:1336–1344
14. Lesburguères E, Gobbo OL, Alaux-Cantin S, Hambucken A, Trifilieff P, Bontempi B (2011) Early tagging of cortical networks is required for the formation of enduring associative memory. Science 331:924–928
15. Kitamura T, Ogawa SK, Roy DS, Okuyama T, Morrissey MD, Smith LM, Redondo RL, Tonegawa S (2017) Engrams and circuits crucial for systems consolidation of a memory. Science 356:73–78
16. Schacter DL, Eich JE, Tulving E (1978) Richard Semon's theory of memory. J Verbal Learn Verbal Behav 17:721–743
17. Lanahan A, Worley P (1998) Immediate-early genes and synaptic function. Neurobiol Learn Mem 70:37–43
18. Guzowski JF, McNaughton BL, Barnes CA, Worley PF (1999) Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. Nat Neurosci 2:1120–1124
19. Reijmers LG, Perkins BL, Matsuo N, Mayford M (2007) Localization of a stable neural correlate of associative memory. Science 317:1230–1233
20. Ramirez S, Liu X, Lin P-A, Suh J, Pignatelli M, Redondo RL, Ryan TJ, Tonegawa S (2013) Creating a false memory in the hippocampus. Science 341:387–391
21. Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484:381–385
22. Cowansage KK, Shuman T, Dillingham BC, Chang A, Golshani P, Mayford M (2014) Direct reactivation of a coherent neocortical memory of context. Neuron 84:432–441
23. Sheng M, Greenberg ME (1990) The regulation and function of c-fos and other immediate early genes in the nervous system. Neuron 4:477–485
24. Richards BA, Xia F, Santoro A, Husse J, Woodin MA, Josselyn SA, Frankland PW (2014) Patterns across multiple memories are identified over time. Nat Neurosci 17:981–986

Meenakshi P completed her MS in Biological Sciences from Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, in 2015. Currently, she is a CSIR senior research fellow at the Centre for Neuroscience, Indian Institute of Science, and she is working with Dr. Balaji Jayaprakash. Her research focuses on how memories transform and become generalised over a time. She is studying this at multiple scales ranging from behaviour to neurons.

Balaji Jayaprakash completed his PhD from Tata Institute of Fundamental Research, Mumbai. He devised and used various optical as well as spectroscopic methods to study the monoamine release dynamics in live neuronal cell for his doctoral studies. During his postdoctoral studies with Prof. Ryan at Weil Medical College, he studied the synaptic vesicle endocytosis and recycling in the central nervous system neurons. Later working with Prof. Silva during his second postdoctoral research at UCLA, he was interested in understanding the mechanisms of memory allocation. Currently, he is an Assistant Professor at the Centre for Neuroscience, IISc. His laboratory is interested in understanding the role of prior knowledge in problem solving. More specifically, his laboratory is interested in understanding the role of remote memory and how it influences our behaviour.