Multiple Memory Systems in the Brain

Sigmund Hsiao[1] and Sin-Chee Chai[2]

Abstract- The brain registers our experience; personal encounters (episodic memory), the facts about our world (semantic memory), many habits and skills (procedural memory), and also the painful and scary encounters (emotional memory). Various subcortical and cortical circuitries are dedicated to the formation and retrieval of these memories. The memory processing can be disrupted with specific brain damage, pathologically or experimentally induced. The disruption is highly selective: certain brain damage interferes with some memories but leaves other memories intact. This article introduces the functional demarcation of memorization and the neural mechanisms. The available data support existence of the triple memory systems in the brain that work independently and in parallel fashion: (a) the hippocampus-declarative memory system, (b) the striatum-procedural memory system, and (c) the amygdala-emotional memory system. These systems often interact to weaken or strengthen the memory retrieval.

Key Words: Declarative memory, Procedural memory, Emotional memory, Parallel systems, Hippocampus, Striatum, Amygdala

老馬識途

管仲、從桓公而伐孤竹，春往冬返，迷惑失道。
管仲曰：『老馬之智可用也。』
乃放老馬而隨之，遂得道行。

【春秋】

"The old horses know the way"

"One spring around 720 B.C., Kuang-Chung traveled with the Emperor Huan to conquer the Ku-Chu province. When winter came they set out for home but could not find the way back. Kuang-Chung advised the Emperor to rely on the old pack horses they had brought with them. They released the horses and followed them and soon realized that they were on the correct path back to their home province.".

Choon-Chiu

From the [1]Department of Psychology, National Chung Cheng University, Chia-Yi, and Institute of Behavioral Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Institute of Biomedical Sciences, Academia Sinica, Taipei, and Department of Psychology, Chung Shan Medical University, Taichung, Taiwan.

Reprint requests and correspondence to: Sin-Chee Chai, PhD. Institute of Biomedical Sciences, Academia Sinica, Taipei, and Department of Psychology, Chung Shan Medical University, Taichung, Taiwan.

INTRODUCTION

The above story from Choon-Chiu, quoted from Chai[1], tells us vividly that the horse had good navigation ability. This may remind a neurologist of Alzheimer's patients who often get lost; probably the horse (or a pet dog) could get them home. Indeed, the navigation requires many forms of the space memory as indicated by Pai[2,3]. This article is about the following questions: How is the memory stored in our brain? Do we have many forms of memory?

The brain's control of the sensory input and motor output functions have been analyzed in great detail at the basal levels. When we pursue further into the higher sensory and motor areas, however, we start to see the functions less and less directly related to the input and output functions. Enough data have been collected in the past decade to start to understand the brain's control of many "intermediate" functions that are related to our concept of "mind": perception, attention, feeling, memorization, emotion, motivation, rewarding, reasoning, language, etc. A large part of modern neuroscience is dedicated to the study of these psychological functions. In a just published textbook of "Fundamental Neuroscience"[4], for example, the section on "Behavioral and Cognitive Neuroscience" occupies a prominent portion and it can be foreseen that the analysis of "mind" will become even more prominent in neuroscience.

The brain encodes the sensory experience from the external (surrounding milieu) and the internal (visceral afferents and muscle feedback) sources and stores as temporary and permanent memories in a highly organized fashion. The memory is retrieved according to the existing internal and external environmental conditions to determine the behavioral output to promote the individual's adaptation (e.g. to escape from or avoid the source of injury before one gets injured, and to approach the source of food and potential mates). This article introduces the triple memory processing theory of the brain.

MEMORY AND THE BRAIN

Memorization, like many functions of our body, is so much a part of our daily life that we take it for granted. The brain has robust and reliable memory processing systems that work automatically without much conscious effort. However, the memory function of the brain differs from other bodily functions in a way that this is a continuously expanding process; the new neural connections that are involved in memory formation appear to form throughout one's lifetime. Our memory brain is a continuously updating system, registering new experiences and reorganizing the entire memory structure, unless selective parts of the brain are damaged.

We used to regard the memory to be like an encyclopedia where every thing is registered in a huge volume and we keep on adding new entries. The brain function in learning and memory was once thought to be "a mass action" and "equipotential"[5], i.e., the larger the brain damage the greater the deficit in learning and that the areas of brain lesion does not matter. However, now we regard the memory to be of multiple formats because clinical and experimental observations indicate that a discrete damage produces deficit in one memory type but spares other types of memory. We now regard that there are three main types of memory: declarative (episodic and semantic), procedural (skill), and emotional. The "episodic memory" is related to the personal encounters; such as where we went and when and what we did. The "semantic memory" is related to the events of the past and present world; such as who is our president and where is Iraq. These are the "knowledge" that we study in schools and read in newspapers. Sometimes we need a little extra effort to rehearse to memorize and retrieve the knowledge. The "procedural memory" is related to what we can do; such as to swim, to ride bikes, play chess, play golf, etc. This memory involves the relationship between a set of environmental stimuli and our motor control and is a stimulus-response learning. The "emotional memory" makes us respond emotionally or fearful to certain stimuli or circumstances[6]. The science of memory function is one of the most challenging enterprises ever taken up by the human brain. Can our brain understand the brain?

EVOLUTION OF THE BRAIN AND ITS MEMORY FUNCTION

The primitive brain is consisted of several modules that directly control sensory and motor functions; the chemosensory module responds to various molecules in the environment, the visual module responds to light energy, and the motor module controls the movements. A creature with this brain responds linearly to the stimulus; the stronger the stimulus the stronger the response. This organism is adaptive, but only within a limited niche. Upon these basic modules the evolution added the thalamus allowing combinations of stimuli to guide the response. The amygdala is added such that a weak stimulus may elicit emotion to provoke a disproportionately strong response, thus, the stimulus-response relationship is no longer "linear". The hippocampus is added such that the stimuli from the past now influence the response outcome making the response even less "linear" to the present stimuli. The hypothalamus is added to organize internal and external stimuli making the behavior more sophisticated, responding to complex combinations of stimuli. The reticular formation is added to control arousal and attention. On the top of all these modules, the cortex is added to serve as the organizer to pull all modules together. The prefrontal cortex plays the role of the "orchestra conductor" that puts together the expertise of many modules to come out with complex behaviors. In Home sapiens, the speech function is added to make the inter-individual and intra-individual communication even more voluminous and timeless. Memory makes it possible for the long and recent past to influence the present, and the present to influence the future. Memory modifies the relationship between the stimulus and response; without it the behavior would be forever like a typical dose-effect curve of a drug, day after day, generation after generation[7].

FROM PHILOSOPHICAL INQUIRY TO EXPERIMENTAL STUDY

Memory has been an important topic in the philosophy of mind. We are familiar with Chinese and Western philosophers who debated whether a person was (a) born to be good, (b) born to be bad, or (c) born to be neither good nor bad and to be good or bad is determined entirely by the experience. The debates went on with each position finding evidence, pro and con. Phrenologists believed that different areas of the brain control different mental functions, like intelligence and temperament, and the bumps of the skull reflected the working of the underlying brain structures. Since about a century ago learning and memory have become a topic under scientific scrutiny. Ebbinghaus presented empirical laws of the memorization and his famous "forgetting curve" through experimentation[8]. Pavlov (Nobel laureate) found that a stimulus and a response could become connected through an associative experience[9]. Tolman argued for the "cognitive map" formation in spatial learning[10] but Skinner[11] and Hull[12] argued for strict stimulus and response connections. Hebb (1949) proposed a model of long-lasting neural events related to associative learning now known as "Hebbian rules"[13] and Kandel (Nobel laureate) delineated the neural plasticity of sensory experience using simple aplysia's nervous system[14]. Broca and Wernicke characterized the language dysfunction with damage to specific areas of the brain. More recently we saw the celebrated amnesic case of H.M. that launched the theory of multiple memory systems[15]. Neuroscientists have been manipulating the animal brain with discrete lesioning and pharmacological techniques (mostly in monkeys, rats and mice) to study neural substrates of learning and memory[7]. The resultant of all these efforts of more than one hundred years culminated in a new theme of "cognitive neuroscience of memory"[4,6,7,16,17].

CURRENT STATUS OF MEMORY RESEARCH

The amnesic case of a patient "H.M." (his initials) illustrates vividly how crucial the detailed phenomenology provided by clinicians is for further scientific analysis. The story started in 1933 with a seven year old boy, who was knocked down by a bicycle and unconscious for five minutes. Three years later he had minor seizures and, at age 16, a major seizure. The seizure became more and more frequent with 10 minor attacks and a

major attack each week. Large doses of anticonvulsant did not work. Dr. Scoville then performed the bilateral medial temporal lobe resection that included all tissues bordering the lateral ventricles; the anterior two-thirds of the hippocampus, the amygdala and the surrounding cortex (see 14 p.87 for details). The surgery was a success and the seizure was largely preventable through medication, but then a totally unexpected consequence was observed. Part, but not all, of his mental capability was lost: (a) his perceptual, motor, and cognitive functions were intact, (b) the memories acquired in childhood were intact, (c) the immediate memory was normal, however; (d) he could not form any declarative (episodic and semantic) memory, although (e) he could form skill memory. For example, H.M. improved his skill after practicing a "mirror drawing" task, but he was unable to recall that he ever did the drawing (episodic memory). This highly selective loss of memory indicated specific neural compartmentalization of the memory function. The analysis of memory function has been focused in the medial temporal lobe to specify what and what not were controlled by this area[18].

A LOOK AT THE MULTIPLE MEMORY SYSTEMS

The H.M. case triggered tremendous number of animal and human studies. Crucial to the studies was the introduction of experimental tasks that reflected the function of a specific brain circuitry. These tasks, may be termed "hippocampus-specific", "striatum-specific" or "amygdala-specific", are used to identify, dissect and isolate the brain's functional and anatomical module like a sharp scalpel that neatly dissected the crucial anatomical locus. The fruit of the effort is the discovery of function-specific neural circuitries of memory: (a) the declarative memory system of the hippocampus, parahippocampus and cerebral cortex, (b) the procedural memory system of striatum and cerebral cortex, and (c) the emotional memory system of amygdala and cerebral cortex. The three systems are "parallel memory systems" because they may be activated simultaneously to encode the three aspects of an event that an individual encounters[7,19]

DISSOCIATION OF MEMORY SYSTEMS IN THE BRAIN

The dissociation effect occurs when a particular kind of memory is uniquely mediated by a particular system. The logic of this effect requires that the lesion or deactivation of brain area A impairs behavior X, but has no effect on behavior Y. At the same time, the lesion of brain area B impairs behavior Y, but has no effect on behavior X. This pattern of results is taken to suggest that A is required specifically for X, and B for Y. This specificity, involving two areas and two behaviors, is termed "double dissociation". If the study involves three brain areas and three behaviors then the specificity is termed "triple dissociation". This is exactly what was shown in the following experiments that resulted in the concept of the triple memory systems.

A critical experiment to dissect the memory systems: McDonald and White[20] at McGill University used three tasks (the variants of the eight-arm radial maze task) to demonstrate in rats a triple dissociation specific to hippocampal lesion, striatal lesion and amygdala lesion. Their versions of the radial arm maze had the same general set-up, the same approach response and food reward, but differed in the stimulus-respond-reward contingencies. The contingency difference necessitated the subjects to adopt different "strategies" to obtain the reward and each strategy required different memory processing. Task 1 required a "win-shift" strategy of remembering where they went to avoid the re-entry error that involved the declarative memory. Task 2 required a "win-stay" strategy of responding to a particular stimulus to obtain food that involved the procedural memory. Task 3 required a "preference" strategy of responding according to where was the rewarded place that involved the emotional memory. Indeed, the lesions to the hippocampus, striatum or amygdala impaired the acquisition of only Tasks 1, 2 and 3, respectively. Based on this experiment and subsequent work in White's laboratory, a multiple parallel memory systems model was born[21].

A unique brain function can be defined by a specific task demand and the following conclusions are reached by the experiments adopting this brain-task combination: (a) The hippocampus controls the memory of what one

did and where (episodic and place type memory), (b) the striatum controls the stimulus-response habit of the cue-guided behavior (response type memory), and (c) the amygdala controls the emotional and incentive memory of "liking and disliking"[22,23]. Furthermore, it has been shown that the effect of hippocampal damage is a temporally graded retrograde amnesia in monkeys, rats and mice. Thus, the sooner the damage after learning tasks the more the amnesic effect. This indicates that hippocampus may be involved in memory consolidation processes rather than its storage[24].

HUMAN STUDIES

In a study by Squire and Cohen (1980), published in "Science", the amnesic patients with various etiology and normal control subjects were trained to learn pattern-analyzing mirror reading skill. During the experiment, unrelated word triplets were presented in a mirror-reversed form to the subjects through a tachistoscope. The subjects were asked to read each word aloud as quickly as possible. All subjects showed normal reduction in reading time across trials. The two groups showed similar reduction in reading time of non-repeated words, which depended on the rules and procedures involved in mirror reading. The normal control subjects, however, showed better performance on repeated triads, which depended on memory for the specific words that were repeated from trial to trial. Upon being questioned, however, none of the amnesic patients reported that words had been repeated during the task even though some words had been presented 20 times[25].

Recent human "dissociation" experiments:

Bechera, Tranel, Damasio, Adolph, Rockland and Damasio[26] reported, in Science, a result from three patients with damage to (a) the hippocampus (bilateral hippocampal atrophy due to transient hypoxia due to cardiac arrest), (b) the amygdala (Urbach-Wiethe disease), and (c) both amygdala and hippocampus (bilateral damage due to herpes simplex encephalitis). When presented with the conditioned stimulus of various colors followed by the unconditioned stimulus of a loud noise, the patient with amygdala damage was hampered in acquisition of an emotional conditioning measured with the skin conductance. However, he was able to recall the color and the number of stimuli presented as the conditioned stimulus. The patient with hippocampal damage was hampered in the recall of the color and number of stimuli presented as the conditioned stimulus, but displayed normal emotional conditioning. The third patient was hampered in both the emotional conditioning and the recall of the conditioned stimulus. This result shows a double dissociation between the declarative (recall of the conditioned stimulus) and emotional memories (conditioned skin conductance response).

In another "Science" report, Knowlton, Mangels and Squire[27] compared the early stage Parkinson's patients (with striatal subfunctioning) and the amnesic patients (with hippocampal damage) with a "weather prediction" probabilistic learning task that required the procedural memory to improve. The result showed that the Parkinsonians failed to improve in this learning but were able to recall the content of the task; on the other hand, the amnesic patients improved in this learning but then failed to recall the task content. This shows the double dissociation between the procedural and declarative memories.

Interactions of the memory systems:

The memory systems may interact with each other to strengthen or weaken the memory recall or the behavioral outcome. A well-known effect of the "flashbulb memory", the vivid recall of the episodes accompanied by strong emotional reactions, is an example of the interaction. There are three possible types of interactions among brain memory systems: interference, cooperation and competition. The observation that lesions of the fimbria-fornix (the main efferents and afferents of the hippocampus) improved or facilitated the amygdala-dependent radial maze task is an example of interference between memory systems[28]. Cooperation between two memory systems is suggested by the finding that lesions of both systems impair a task while lesions of either structure alone have no effect. McDonald and White trained rats to run from the center platform of a radial maze into either of two arms separated by some 135 degrees. One arm always contained food, and the other

never contained food. Separate lesions of the fimbria-fornix or dorsal striatum failed to block this type of active place discrimination. However, combined lesions of the fimbria-fornix and dorsal striatum, but not of the amygdala and striatum, or amygdala and fimbria-fornix, impaired it. This result indicated that either hippocampus-based and striatum-based systems is involved in this discrimination task. If one of the systems was impaired, the behavior could be maintained by the other system[29].

Competition between memory systems was also demonstrated in a water maze where rats were trained to swim to both visible and hidden platforms in the fixed locations. On the test trial, the visible platform was moved to a new location. Rats with fimbria-fornix lesions tended to swim to the visible platform in the new location suggesting they were guided by explicit cues (striatum-based memory system). Rats with dorsal striatum lesions, however, tended to swim to the original location of the invisible platform suggesting they were guided by the spatial cues (hippocampus-based memory system). When both systems were intact, these systems competed with each other during the choice of platform such that the rats were observed to vacillate between the two targets, thus, about half the rats chose the visible platform or the invisible platform[30].

Multiple memory systems at work: some research in Taiwan

In our laboratory we studied the emotional memory known as "the contextual fear" in rats. The contextual fear is different from the fear response that is formed as a result of the association between a specific stimulus (sound or light on or off) and an aversive stimulus (momentary foot shock). The contextual fear is formed when rats are confined into a box briefly (about 20 sec) and shocked. Rats will show freezing response (an index of fear) when they re-enter the context. This contextual fear requires two associations: The first association is amongst the stimuli in the context to form the "contextual representation". This is a form of the declarative memory of "that place" and requires the hippocampus. The second association is between this place representation and the shock-induced pain. This association forms an aversive emotional memory and requires the amyg-

dala. We showed that when the hippocampus was deactivated with a GABA agonist (muscimol) or a NMDA antagonist (AP-5) the fear conditioning was hampered. Our result suggested that the amygdala activation inhibited the hippocampus to hamper the formation of contextual representation, i.e, emotion may inhibit acquisition of the declarative memory. The contextual fear is a good example of the interaction between the hippocampus-declarative and the amygdala-emotional memory systems. The understanding of the contextual fear formation gives the explanation of why we might become jumpy (emotional reactions) in a ghost house, that involves a place memory and an emotional memory.

Preliminary study of Chai and his colleagues have shown that the anterior cingulate cortex (ACC) is involved in mediating the short-term memory but not the long-term memory components in an inhibitory avoidance learning task. ACC lesion impaired the passive avoidance retention tested 30 seconds after electrical footshock but remained intact if the test was given after 24 hours. The 24 hour retention test was, however, impaired by medial thalamus lesions. These findings indicate that ACC may be important for the aversive short-term memory, but not for long-term memory. Medial thalamus may be the essential gateway leading to the acquisition and consolidation of both types of aversive memory.

CONCLUDING REMARKS

Each of the triple memory systems can be considered as a module that has its own intricate inner neural circuitry. Each memory module is comparable to the well-known module of the hypothalamus- pituitary-adrenal cortex (HPA) axis of the stress reaction or the hypothalamus-pituitary-gonads (HPG) axis of the control of reproductive cycle. The memory module is activated by the external and internal environmental input and an organism reacts to the present by incorporating its past experience to promote the survival of individual and its species. The prefrontal cortex may control the retrieval of multiple memory components from the cortical memory storage to form the working memory with subsystems of visuospatial sketch pad (for nonverbal

images) and phonological loop (for speech perception and subvocal rehersal of verbal materials) that lasts as long as the task at hand is being processed[31]. The retrieved memory, together with the changing external and internal stimuli related to the moment-to-moment performance-related feedback, are processed in the sub-cortical regions to fine-tune the output. The memory systems provide the machinery to transcend the time and space limitation and to create a new, even more suitable, environment for the organism's well being. So, our memory is more than an encyclopedic collection of facts. It is continually working, unpdating and creating. Thus, the human brain can unravel the secret of all the brains, including the species' own. But, there is a lot more yet to be done.

ACKNOWLEDGEMENTS

REFERENCES

1. Chai SC. The Functions of Amygdala and Hippocampus in Conditioned Cue Preference Learning. McGill University, Montreal, Canada. Doctoral Dissertation, 2002.

2. Pai MC. Navigation Ability in Advancing Alzheimer's Disease Patients. National Chung Cheng University, Chiayi, Taiwan. Doctoral Dissertation, 2002.

3. Pai MC, Hsiao S. Incipient symptoms of Alzheimer's disease and effect of education on the onset age: a study of 155 Taiwanese patients. Acta Neurol Taiwan 2002;11:66-9.

4. Squire LR, Bloom FE, McConell SK, et al. Fundamental Neuroscience. New York: Academic Press, 2003.

5. Lashley KS. In search of the engram. Cambridge, England: Cambridge University Press, 1950.

6. Milner B, Squire LR, Kandel ER. Cognitive neuroscience and the study of memory. Neuron 1998;20:445-68.

7. Carter R. Mapping the Mind. University of California Press, 1998.

8. Ebbinghaus H. Memory: A Contribution to Experimental Psychology. New York: Dover. (Original work published in 1885), 1935.

9. Pavlov IP. Conditioned Reflex. Oxford: Oxford University Press, 1927.

10. Tolman EC. Cognitive maps in rats and men. Psychol Rev 1948;55:189-208.

11. Skinner BF. The Behavior of Organisms. New York: Appleton-Century-Crofts, 1938.

12. Hull CL. Principles of Behavior. New York: Appleton-Century-Crofts, 1943.

13. Hebb DO. The Organization of Behavior. New York: John Wiley & Sons, 1949.

14. Kandel ER, Schwartz JH, Jessell TM. Cellular mechanisms of learning and memory. In: Kandel ER, Schwartz JH, Jessell TM, eds. Essential of Neural Science and Behavior. Norwalk, CT: Appleton & Lange, 1995.

15. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957;20:11-9.

16. Eichenbaum H. The hippocampus and mechanisms of declarative memory. Behav Brain Res 1999;103:123-33.

17. Eichenbaum H. The Cognitive Neuroscience of Memory: an Introduction. New York: Oxford University Press, 2002.

18. Milner B. Memory and the medial temporal regions of the brain. In: Pribram KH, Broadbent DB, eds. Biology of Memory. Academic Press, Inc, 1970:29-50.

19. Kesner RP. Neurobiological views of memory. In: Martinez JL, Kesner RP, eds. Neurobiology of Learning and Memory. San Diego, CA: Academic Press, 1998:361-416.

20. McDonald RJ, White NM. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci 1993;107:3-22.

21. White NM, McDonald RJ. Multiple parallel memory systems in the brain of the rat. Neurobiol Learn Mem 2002; 77:125-84.

22. Packard MG, Hirsh R, White NM. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J Neurosci 1989;9:1465-72.

23. Cho YH, Beracochea D, Jaffard R. Extended temporal gradient for the retrograde and anterograde amnesia produced by ibotenate entorhinal cortex lesions in mice. J Neurosci 1993;13:1759-66.

24. Packard MG, McGaugh JL. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expres-

176

sion of place and response learning. Neurobiol Learn Mem
1996;65:65-72.

25. Cohen NJ, Squire LR. Preserved learning and retention of
pattern-analyzing skill in amnesia: dissociation of knowing
how and knowing that. Science 1980;210:207-9.

26. Bechara A, Tranel D, Damasio H, et al. Double dissociation
of conditioning and declarative knowledge relative to the
amygdala and hippocampus in humans. Science 1995;269:
1115-8.

27. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit
learning system in humans. Science 1996;273:1399-402.

28. White NM, McDonald RJ. Acquisition of a spatial condi-

tioned place preference is impaired by amygdala lesions
and improved by fornix lesions. Behav Brain Res 1993;55:
269-81.

29. McDonald RJ, White NM. Hippocampal and nonhippocam-
pal contributions to place learning in rats. Behav Neurosci
1995;109:579-93.

30. Devan BD, White NM. Parallel information processing in
the dorsal striatum: relation to hippocampal function. J
Neurosci 1999;19:2789-98.

31. Baddeley AD. The fractionation of working memory. Proc
Natl Acad Sci U S A 1996;93:13468-72.