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Working Paper No. 343 May, 1995

A Brief Review of Memory Research in Cognitive Neuroscience

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Abstract

I would have liked to start this paper by first presenting a coherent model of human memory. After describing the functional components of the model and the structural components of the model, I would review the studies that provide evidence for each component and the interrelations between the components. After several sleepless nights, I gave up on this dream. And I decided that it was not my fault. The main reason why it is not my fault is that if such a coherent model was deducible from the data collected so far, one of the many intelligent people who devoted life times on this ideal would have come up with it. Unfortunately the data is sketchy. It highlights a few pieces here, and a few pieces there. Not only are the connections between different findings poorly understood, in most cases the interpretation of a single finding is still under debate. Given this picture, my review could mirror nothing but the sketchy character of the available data.

1 Introduction

The word "memory" is misleading. Being a single word, it creates the impression that it refers to a single entity. The same criticism applies to most of the terms of naive psychology, such as intelligence, or self. Only after one tries to understand the workings of memory, that one realizes the inadequacy of this common sense notion. Memory is not unitary. There are many dimensions along which different types of memory can be classified. Memory does not exist at a single place. It seems like almost every sub-system in the brain has its own memory. In some sense, memory should be an adjective, rather than a noun, denoting a quality that a particular system may or may not have.

Being such a diffusely linked union of mechanisms, how did people come up with such a concept and initiate research efforts to understand it? Maybe it is not because people are bad at creating concepts, in fact they are the best at that in the world. It is because of this miraculous illusion, a sense of unity that one subjectively feels, when one thinks about how his mind works. If one has a fully functional mind, most of the time one does not realize how effortlessly the important details of the life are stored, how just the relevant information is retrieved when a problem is to be solved. It is only after something breaks down that this illusion goes away, and we start seeing the signs of the interlocked mechanisms, normally working together in harmony, to create this illusion of memory for us.

It is said that learning is the crown of intelligence. After all, computers are performing complex computations everyday, that would take people years to complete. However, even the best performing chess program does not get any better from one game to the next. It is this potential of learning, the ability to excel in any field we choose, that makes us intelligent. And learning is what memory does. Thus for a full understanding of how the mind works, it is essential to solve the mysteries of memory.

2 History

The roots of many sciences can be found in philosophy. This is hardly surprising since until recent times philosophy and science (and even religion) did not have clear boundaries between them. Psychology is no exception. The topic of memory has been a topic of interest to philosophers since the times of the ancient Greek. Every philosopher since Plato and Aristotle that became interested in the question of mind, had to face the problem of memory. After all, the field of epistemology, or the science of knowledge, is inherently linked with our understanding of memory.

In the beginning of the nineteenth century, the French philosopher Maine de Biran wrote a monograph entitled "The influence of habit on the faculty of thinking" [de Biran, 1804]. He observed that habits were developed by repetition and resulted in increased automaticity of execution and decreased conscious awareness. He acknowledged the fact that there could be different kinds of memory. He postulated three different kinds, which he referred to as mechanical memory, sensitive memory and representative memory. Mechanical memory is involved in acquisition of motor and verbal habits that operate at an unconscious level. Sensitive memory is involved in acquiring feelings, affects and fleeting images, and it too operates at an unconscious level. The representative memory is what performs the conscious recollection of facts and ideas. Given the lack of knowledge and empirical data of his time, this was a rather remarkable account.

The phrenologists of the mid nineteenth century, although later dismissed because of their wrong conclusions based on correlating high level behavioral traits with bumps on the skull, actually had some respectable observations and theories about the workings of the mind. Franz Joseph Gall focused on the differences in the type of information handled by different forms of memory. He contrasted between two different types of faculties. First content or domain specific modules that operate on particular kinds of information. The other type cuts across content domains, such as unitary faculties of memory, judgment, perception and so forth. Gall commented that "Perception and memory are only attributes common to the fundamental faculties, but not the fundamental faculties themselves" [Gall, 1835]. Spurzheim elaborated Gall's ideas and argued that each mental faculty has a separate memory, relying on observations of within individual variations in memory abilities [Spurzheim, 1834].

Next comes the path breaking studies of physicians Broca and Wernicke on the language areas of the brain based on the studies of patients with brain lesions. Although these studies were influential for neuropsychology in general, they also have relevance as evidence for different faculties of memory. The ability to articulate words is learnt in childhood. In his classic work, Broca commented "Is it not, after all, a kind of memory, and those who have lost it have lost, not the memory for words, but the memory of the procedures required for articulating words" [Broca, 1861].

Ewald Hering, in his famous 1870 lecture at the Vienna Academy of Sciences emphasized the role of memory in cognition as a unifying force that holds the self together [Hering, 1920]. He proposed the concept of an "organic memory" involved in heredity, development, and habit. William Carpenter, in one of the earliest treatises on physiological psychology [Carpenter, 1874], argued that motor memory or habit should be distinguished from recollection of personal experiences.

The famous American psychologist William James, in his 1890 classic "Principles of Psychology" [James, 1890] treated memory and habit in separate chapters. He also distinguished between what he called primary memory, one that endured for a very brief time, and secondary memory, "the knowledge of a former state of mind after it has already once dropped from the consciousness". It is surprising that, not until 1958 [Broadbent, 1958]were separate short-term and long-term memories specifically postulated.

Although a number of scientists had been collecting data and theorizing about memory, it is not unfair to say that Hermann Ebbinghaus set the stage for a century long sequence of studies for the analysis of memory. The methodology he presented in his 1885 book "Uber das Gedachtniss" - the use of nonsense syllables as to-be-remembered materials, the savings method etc. - influenced generations of researchers. He laid out an experimental agenda that included such problems as repetition effects, remote associations, massed versus distributed practice, and the like. The merits and drawbacks of the Ebbinghausian influence on the psychological analyses of memory have been debated since the early years of memory research. However one should remember that he developed his methodology more than a century ago, in a setting where not much data was available. It is unfair to give him the responsibility if some later researchers were too slow in breaking out of the limits he had set. Ebbinghaus still is regarded as the father of the cognitive science of memory.

At the turn of the century, Freud published his much debated theories on psychoanalysis [Freud, 1900]. Although much of what he had said is dismissed because of being unscientific, and never mentioned in the contemporary cognitive science courses, he did have interesting hypotheses about the workings of the mind. Memory played quite an important role in his psychoanalytic theory. He most clearly emphasized the distinction between conscious and unconscious and drew the attention to the effect of infantile memories on a person's mental health and value judgments. Compared to Ebbinghaus, he tried to theorize about phenomena way ahead of his time scientifically, but this does not mean that the same questions he asked will not turn around and face science again.

In the late 1800s, a Russian physician, S. S. Korsakoff, reported on a syndrome he found with chronic alcoholics. Korsakoff's syndrome was to play an important role in the future studies of memory, since it is one of the most isolated cases of amnesia. Patients with Korsakoff's syndrome have normal IQs, are alert and attentive, appear motivated, and generally lack other neurological signs of cerebral deficit. This is in contrast with their extensive retrograde and anterograde amnesia.

The debate between globalism and localizationism in psychology was still heated in the beginning of the twentieth century. Globalists believed that the brain functioned as a single, integrated whole, localizationists believed that the brain was a collection of distinct organs, each responsible for a separate ability. The neuropsychological study of memory is rooted in this debate. Karl Lashley started a lifetime project in 1915 to identify the neural locations of learnt habits. In most of his experiments he removed portions of or made lesions in the cortex of animals. After decades of experimentation he was unable to localize specific memories in the brain. In 1950 he concluded that "it is not possible to demonstrate the isolated localization of a memory trace anywhere in the nervous system. Limited regions may be essential for learning or retention of a particular activity, but ... the engram is represented throughout the region" [Lashley, 1950]. Ironically, only three years later a neurosurgeon named William Scoville made one of the most influential discoveries of neuropsychology. He removed the hippocampus bilaterally from patient H. M. to cure his epilepsy and unexpectedly created the most famous and most studied subject of amnesia in history.

In the meanwhile studies in the cognitive science of memory were independently pursued by researchers such as Miller [Miller, 1956] and Sperling [Sperling, 1960]. These researchers concentrated on short term memory, and were influenced by the Ebbinghausian tradition at the methodological level. The predominant approach to long term memory in this era had been the associative interference theory, which emphasized the importance of relatively automatic and passive formation of stimulus-response bonds. Studies against this hypothesis were seen from time to time such as the work of the British psychologist Frederic Bartlett [Bartlett, 1932]. Bartlett proposed schemas - organized mental structures - as the key element in remembering. He emphasized that memory is a process of active reconstruction rather than a mere revival of previous experience. Associationist approach was finally taken over by organization theory and related cognitive approaches that highlighted the active and constructive nature of the mnemonic processes after the work of researchers such as Tulving [Tulving, 1962] and Mandler [Mandler, 1968]. Until very recently, the cognitive science of memory have been largely developed independent of the neuroscience perspective, and researchers have done little to connect their theories to neural matter. Since this review is focused on the neuroscience, I will not dive into any more detail of the pure cognitive approach.

One last bit of history I would like to go into before I close the section is the work of Hebb [Hebb, 1949]. Hebb went a step further from the behavioral data and developed a theory of the neurological basis of short-term and long-term memory in his classical book "Organization of Behavior". He invented Hebbian learning rule that models the change in a neural network by repeated experience. His principles with minor modifications were later verified by the discovery of long term potentiation in real neurons. One generation before Hebb, neuroanatomists Cajal and Golgi were still debating whether neurons are individual units or form a continuous structure. Hebb attempted to explain psychological events by the physiological properties of the nervous system. His work still remains the best attempt to combine the principles of psychological reality and the facts of neuroscience.

3 Cells

In his much cited work Marr stressed the idea that psychological phenomena can be understood at multiple levels of analysis [Marr, 1982]. He separated what is computed, how it is computed and the level of implementation from each other. Although this distinction clarified the way of thinking in some domains, it did not help too much in others. Frequently, the hardware level determines the most efficient way to compute something, and what an organism does is limited by what it can compute efficiently. Thus these three layers cannot be separated productively from each other. Cognitive neuroscience in particular tries to bridge the gap between these three levels wherever possible. Keeping this spirit, I found it appropriate to start the discussion of memory at the level of neurons.

Hebb combined the associational-learning theory of Clark Hull and his contemporaries in the 1930s and 1940s with what was known of nervous system activity at his time, to describe the basis of learning and memory. He separated short term memory from long term memory. He described short term memory as an active process of a short duration, whereas long term memory involved structural change in the nervous system.

Hebb hypothesized that if one neuron frequently takes part in exciting another, some growth process or metabolic change takes place in one or both cells and the strength of their connection increases. Thus the neurons become linked functionally. In his view, the cell assemblies organized to process perceptual information were capable of continuing their activity after the stimulation has ceased. This repeated activation after the initial sensory input was necessary to produce the structural changes for the long term memory. These repeated reverberations formed the short-term memory. Furthermore, for the structural synaptic changes to occur, there must be a period in which the cell assembly is left undisturbed. Hebb called this period the consolidation, which might take from 15 min to an hour. The amnesia of events just prior to a concussion are the evidence for this process. Finally, Hebb hypothesized that any cell assembly could be excited by others. So particular thoughts could occur in the absence of the original event they correspond to. This was the basis for thought and ideation.

The work by Bliss, Gardner-Medwin and Lømo demonstrated the phenomenon of long term potentiation [Bliss and Lomo, 1973]. They electrically stimulated perforant path fibers to the dentate area of the hippocampal formation of rabbits. They measured the magnitude of the response of cells that are known to receive projections from the stimulation area using microelectrodes. Their basic finding was that increasing the frequency of stimulation for a short period of time resulted in potentiation. Potentiation can be defined as increased sensitivity of the receiving area. Immediately after the high frequency stimulation they observed a gradually declining increase in the response of the recipient cells. This is a transient effect and is known as posttetanic potentiation. More importantly, even though this high magnitude response decreases gradually, it does not necessarily return to the baseline and remains at an elevated level. This is known as long term potentiation, or LTP for short. Although the phenomena of posttetanic potentiation and LTP have strong appeals as explanations of short term and long term memory, they are low level mechanisms, and they do not explain architecture level phenomena such as differential effects of lesions in different parts of the brain.

The molecular basis of LTP is beginning to become clear. Although the trigger for LTP is generally agreed to occur in the postsynaptic cell, the site at which it is expressed is still disputed. Some authors have suggested that the mechanism of LTP is enhanced neurotransmitter release, others that it is increased postsynaptic sensitivity to transmitter, and still others believe that both maybe the case. Bekkers and Stevens report a molecular mechanism that behaves similarly via a pre-synaptic mechanism [Bekkers and Stevens, 1990]. Their analysis of the statistical properties of synaptic transmission, before and after the induction of long term potentiation, suggest that expression of LTP largely arises in a presynaptic mechanism - an increased probability of transmitter release.

It is also possible that structural changes in neurons underlie some forms of memory and learning. In an extensive set of experiments by Greenough and his colleagues it has been shown that when animals are trained for specific tasks or exposed to specific environments there are changes in the dendrites of neurons [Greenough and Chang, 1985]. Greenough has shown that an increase in the number of dendrites is accompanied by an increase in the number of synapses, which might account for functional changes. In addition, the quality of the synapses, new or old, are known to change in long term potentiation. Although the exact mechanisms for these changes are still being discovered, it seems clear that behavioral change stems from morphological changes in neurons.

Studies on simple animals to discover the neural underpinnings of learning has made significant contributions to our understanding of the mechanisms of memory. Hawkins and Kandel suggested that higher forms of learning may be based on the mechanisms of simple forms of habituation, sensitization and conditioning [Hawkins and Kandel, 1984]. Studies on the invertebrate Aplysia showed that the siphon withdrawal reflex in this animal is an extension of the mechanism underlying sensitization. Similarly, Hawkins and Kandel showed how several higher order features of classical conditioning, including generalization, extinction, second-order conditioning, blocking and the effect of contingency can be accounted for by combinations of the cellular processes that underlie habituation, sensitization, and classical conditioning. The Hebb synapse is only one possible way in which neural networks could learn. Hawkins and Kandel described a different mechanism that does not depend on simultaneous events in pre-synaptic and post-synaptic neurons, but rather rely on neurochemical events within the sending neuron.

Gluck and Thompson studied the phenomena in Alypsia using a computational model [Gluck and Thompson, 1987]. They developed a computational model of the neural substrates of elementary associative learning, using the neural circuits known to govern classical conditioning of the withdrawal response of Alypsia. This study proved the importance of actually building computer models that allow the researchers to see the dynamic interactions. Gluck and Thompson discovered several shortcomings of the model created by Hawkins and Kandel and suggested new directions of research. This work demonstrates clearly that the human brain is very bad at simulating complex systems reliably. When any non trivial model of a complex system passes the level of vagueness, and becomes a precise specification of the mechanisms, it is important to start using computer models to observe counter-intuitive results that emerge out of the complexity.

Ambros-Ingerson and colleagues worked on a simulation of the olfactory learning in rabbits using the same principles as Gluck and Thompson [Ambros-Ingerson et al., 1990]. They modeled layers I and II of the olfactory paleocortex, as connected to its primary input structure, olfactory bulb. They demonstrated that long term potentiation by means of repetitive sampling of inputs caused the simulation to organize encodings of learned cues into a hierarchical memory that uncovered statistical relationships in the cue environment, corresponding to the performance of hierarchical clustering by the biological network. These findings suggest that similar principles of learning may govern how networks store information in different neural systems. Different systems have different physical organization of the neurons and different input and output relationships, but the same learning principles may apply to them in general.

Barto and Jordan proposed a novel learning algorithm for neural networks that might be biologically more plausible than the standard back propagation [Barto and Jordan, 1987]. The standard algorithm for learning in artificial neural networks involves comparing the output of the network with the desired output, and propagating the gradient of the error backwards through the connections to make the network gradually approach the desired setting. This method performs well for using neural networks to solve artificial problems of classification and recognition, however it is unreasonable to expect the existence of a "desired output" oracle in nature. The Associative Reward-Penalty algorithm proposed by Barto and Jordan relies on an approximation of the gradient by individual units independently, rather than an exact computation that has to be propagated through the network.

It is generally accepted then, that learning and memory are based on morphological change in the synaptic structure of the neurons. It seems plausible that these changes occur in the systems that process the original information. Kolb discusses three questions that need to be answered if this theory happens to be true [Kolb and Whishaw, 1990a].

The first concern is that neurons in the lower levels of processing, such as primary visual cortex, should not change much, otherwise the information sent to higher areas would be radically different. I think this problem has a natural solution, because low level areas, by definition are exposed to the raw stimuli from the world. As processing progresses to higher levels, these stimuli gradually get recognized and categorized and finally labeled. It seems then the number of different stimuli a higher level has to deal is much more restricted than a lower level. Consider recognizing faces as an example. Even the different perspectives, lighting conditions and distances a single face can be seen from make it highly unlikely for the primary visual cortex to get the exact same impression of a face twice in a life time. However, at some higher level of the visual system, the face is processed, recognized, and labeled as "my mother". At that level of the system, the different inputs one can get is limited by the different number of people one can recognize. Because long term potentiation requires repetition of the input stimuli, it is natural that changes due to learning do not easily occur in a low level system, but memories are usually formed in higher level systems.

Second concern is how we remember ideas and thoughts, if sensory experience is what changes the sensory systems and forms memories. This would not be a concern, if ideas and thoughts are just a complicated mosaic of sensory imaginations, presumably at higher perceptual fields and association fields. There is evidence from the visual imagery work that thinking and perceiving may be using the exact same machinery. If we understand and think in terms of our lower level sensory primitives, we do not need any extra machinery to have memories about our thoughts.

The final question is how we find specific memories, if they are widely distributed in large cell assemblies. This would really be an impossible problem if brain was organized like a computer where processing and memory are in two different locations, connected to each other with a narrow bottleneck. However it does not seem very likely that the same organization exists in the brain. Processing and memory are probably handled by the same underlying hardware. If this is the case, then just as a system can recognize an external stimuli and activate its related parts, it can also recognize an internal stimuli, generated by the activation of another system in the brain. Remembering can be like a chain reaction. A small activation in a single system, maybe caused by an external stimuli, or a previous piece of thought, first activates the related parts of this system. Then this activation grows like a snowball, and connected systems start activating their own relevant memories. It is wrong to restrict oneself to think that something searches inside the head and finds the memories that we want. It is probable that the memories sense when they become relevant and jump into our attention. Given that we hold millions of bits of information at a given time in our long term memory, the fact that we can find anything relevant when we want to think about a particular thing, can only be explained by a parallel processing system of this sort.

4 Behavior

4.1 Patient H. M.

On 23 August 1953, William Scoville performed a bilateral medial temporal lobe resection on patient H. M. in an attempt to stop his epileptic seizures. The result was a surprise to everyone. After the operation, H. M. experienced a severe anterograde memory impairment that persisted to this day. Having been studied for more than 40 years, H. M. can be considered the single patient that has provided the largest collection of data to the students of memory [Corkin, 1984] [Milner, 1968].

H. M.'s syndrome is surprisingly isolated. His impairment is mostly limited to his inability to register new facts in his long term memory. His IQ is above average. His perceptual abilities are normal except his odor discrimination. This is normal, because the operation might have damaged the orbitofrontal cortex, olfactory bulb, or olfactory tracts. Some of his spatial abilities are compromised, and some are preserved. His performance efficiency might reflect the specialization of the temporal neocortex versus the medial temporal-lobe structures. He does not have any attentional disorder. His immediate memory is preserved in both verbal and non-verbal tasks. Although his operation was performed when he was 27, his memories are intact until age 16, with an 11 year retrograde amnesia. His language production and comprehension are mostly normal, he can understand and produce complex verbal material. He is impaired on tests of semantic and symbolic verbal fluency. This might be due to premature aging produced by his multiple neural abnormalities.

There have been dozens of experiments on H. M.'s memory impairment. In his post-operative years since 1953, his symptoms have been very stable. The major findings show that he is impaired at virtually any kind of learning task in which there is a delay between presentation and recall, particularly if interfering material is presented in between. The learning materials used in tests include photographs of people, verbal material, sequences of digits, complex geometric designs or nonsense patterns. He is severely impaired with his memory of daily life. He does not know, for example, where he lives, who cares for him, what he ate at his last meal, what year it is, who the president is, or how old he is. In 1982, he failed to recognize a picture of himself that had been taken on his 40th birthday in 1966. He has some islands of remembering from his post-operative years, however. For example he knows what an astronaut is, a public figure named Kennedy was assassinated and what rock music is. Although H. M.'s general knowledge is meager, it is not completely void.

H. M. has been tested on different maze learning tasks [Milner, 1970]. These are typically tasks in which the subjects tries to learn a path on a board with his fingers. He failed to acquire to correct route even after extensive testing. He was able to learn the solution on a radically shortened version of the test, although after many repetitions.

The attempts of testing classical conditioning on H. M. have failed because of a peculiar reason. The tests by Kimura in 1962 had to be abandoned because H. M. was extremely tolerant to electric shock, even at the levels normal people find painful. This extreme tolerance was later understood to be a manifestation of a more general lack of sensitivity to internal signals such as hunger, pain and fatigue. The structural damage responsible for this is uncertain.

More interesting results are the ones that show the tasks that H. M. can perform. For example the fact that H. M. only has problems with long term memory but has an intact short term memory clearly demonstrate that these two phenomena are supported by different hardware. Furthermore, the fact that H. M. has intact memories from his childhood, but cannot remember anything new shows that the structures that store memories are separate from the mechanisms that encode them, and hippocampus probably plays a role in the latter. There are other dissociations discovered on H. M., most notably the experiments on motor and skill learning. In a 1962 experiment Milner trained H. M. on a mirror-drawing task. This task involves tracing some figure on the paper by only seeing the mirror image of the drawing. Normal people are initially pretty bad at this task, but they can get better with training. H. M. had a normal learning curve for this task. On later days, even though he denied having performed the task previously, he retained his skill. Corkin trained H. M. on various other manual tracking and coordination tasks [Corkin, 1968]. He showed nearly normal improvement from session to session. He could be trained to acquire perceptual skills, such as reading of briefly presented words, or mirror reading. Cohen and Corkin showed a similar result on the Tower of Hanoi puzzle in 1981 [Cohen and Corkin, 1981]. This is a qualitatively different result, since the puzzle involves mental operations beyond just motor coordination or simple perception. H. M. was able to learn the procedures necessary to perform this cognitive skill, even though he did not have any declarative memory of performing the task. Also, biasing effects with words is quite normal. After having been shown a word, although he fails dramatically on subsequent recall and recognition testing, he becomes biased in subsequent word stem completion tasks. The distinction between procedural and declarative learning may be one dichotomy to explain these findings.

4.2 Implicit memory

The biasing experiments with H. M. show a rather different kind of dichotomy; explicit vs implicit memory. Explicit memories can be accessed to guide multiple types of behavior and can rise to consciousness, whereas implicit memories are tied to specific contexts and cannot be accessed deliberately or detected except in special circumstances. Schacter [Schacter, 1987], gives a nice review of the implicit memory research. Savings during relearning, effects of subliminally encoded stimuli, learning and conditioning without awareness, repetition priming effects and findings on amnesic patients like H. M. are some of the evidence for implicit memory.

Shimamura and colleagues studied the effects of word priming in dementia and amnesia [Shimamura et al., 1987]. They tested both word completion priming and verbal memory ability in patients with Alzheimer's disease, patients with Korsakoff's syndrome, and patients with Huntington's disease. Alzheimer's disease causes amnesia because of the degeneration of corticolimbic connections which isolate the hippocampal formation from the rest of the neocortex. Korsakoff's disease have memory impairment due to damage to the diencephalic midline. Huntington's disease prominently affects the basal ganglia and impairs both motor and cognitive functions. All three patient groups exhibited impaired verbal memory on both recall and recognition tests, although Huntington's patients were significantly better than the other two groups. In the word priming task, the Alzheimer's patients were significantly impaired relative to the other two groups. Korsakoff's and Huntington's patients did not show a significant difference from their respective control groups. This probably shows that damage to brain regions in addition to those damaged in amnesia must occur at relatively early stages of the Alzheimer's disease.

Buckner and colleagues analyzed PET scans of subjects during explicit and implicit memory retrieval tasks [Buckner, 1995]. The three different tasks they gave the subjects were explicit recall of previously presented study words, implicit priming effects without intentional recall and a baseline task of retrieval of information from a general knowledge store. Many activations were found to be consistent across experiments. The recall task activated regions in anterior right prefrontal cortex, in addition to areas activated in the baseline condition. In the priming task there was a blood flow reduction in occipitotemporal regions. These experiments suggest that areas of frontal cortex play a role in explicit recall and that an effect of priming may be to require less activation of perceptual regions for the processing of recently presented information.

4.3 Hemispheric specialization

A collection of studies in 1960's and 1970's on patients with unilateral hippocampal lesions show that the two hippocampi can be functionally dissociated. Studies by Milner, Corkin, Corsi and Petrides show that patients with right hippocampus lesions are impaired in tasks such as maze learning, face recognition, spatial block tapping, spatial position, spatial association, spatial memory and self ordered design recall. On the other hand, patients with left hippocampal lesions are impaired at tasks including recall of nonsense syllables, word lists, recurring digits test, non-spatial association, self-ordered word recall, and recall of consonant trigrams.

The maze learning task is similar to the one applied to H. M. The subject is supposed to learn the path in a model maze using visual or tactile clues. The spatial position test involves marking a circle indicated on an exposed 8-in line, then, after a short delay, reproducing this position on another 8-in line. The recurring digits test first invented by Hebb, is an ingenious test that probes the long term memory. First the digit span of the subject is discovered. Then the subject is given groups of digits that are one more than his span. Every third trial, the subject is given the same set of digits. The subject's performance on this recurring set increases with time whereas it stays constant with the random sets. Corsi devised a spatial version of this test, the block tapping. Subjects see several blocks lying on a table. The examiner taps the blocks in a certain order, and the subject is supposed to reproduce this order. Just like the previous test, subjects have a span for blocks. Thus the same experiment can be performed by giving the subjects a repeating sequence every third trial. This test appears to be the best available noninvasive test for right hippocampal function. The patients with right hippocampal lesions do not learn the repeating sequence or do so very slowly.

Studies on patients with temporal neocortex lesions show that this region also plays an important role in memory. Although patients with temporal neocortex lesions do not show global deficits of the sort H. M. does, they do have more selective impairments. Milner and her colleagues have double dissociated the effects of damage to the temporal neocortex of each hemisphere on several memory tasks. Patients with lesions in the right temporal lobe were impaired in the tests of geometric recall, paired-associate nonsense figures, recognition of nonsense figures, recurring nonsense figures, recognition of faces, unfamiliar melodies and tunes. Patients with left temporal lobe lesions were impaired at recall of stories, paired-associate words, recognition of words, numbers, and recurring nonsense syllable tests.

Jones found that patients with left hemisphere lesions could improve their verbal memory by encoding verbal information with the assistance of visual imagery. Similarly, patients with right temporal lesions benefited from the use of verbal encoding. H. M. did not benefit from any of these strategies, indicating that these encoding schemes only help in the existence of one intact hippocampus.

4.4 Other observations

Stimulation of brain regions during neurosurgery is another common method to determine brain function. Chapman and his associates stimulated the hippocampus of several epileptic patients and found that bilateral stimulations produced retrograde amnesia that persisted for a few hours and reached back about two weeks. Immediate memory and other long term memories were intact. However there are problems with the interpretation of these observations. In a series of experiments, Rasmussen and colleagues discovered that there were significant alterations of electrical activity in the temporal cortex following the hippocampal stimulation. Thus the disturbances in memory might be due to the disruption of activity elsewhere in the brain.

Sodium amytal testing is another clinical tool that is used to determine hemispheric function. Discovered by Wada and Rasmussen, this technique involves injection of sodium amytal into the carotid artery to produce a brief period of anesthesia of a single hemisphere. This technique is typically used to determine the speech hemisphere before surgery. The study by Jones-Gotman showed that the technique can also be used to determine the extent of unilateral lesions. Injection of sodium amytal to the contralateral hemisphere leaves the patient with the damaged side, and allows for the measurement of memory deficit.

4.5 Damage to the other areas

Patients with frontal lobe damage do not show the obvious deficits of the temporal lobe patients. However it is recently discovered that frontal lobe lesions cause subtle memory impairments. The first study showing an impairment was done by Prisko in 1963. The task was to tell whether two successively presented stimuli were the same. Different modalities were tried for the stimuli, clicks, lights, tones, colors, nonsense patterns, etc. The difficulty of the task comes from the requirement to suppress the stimuli from previous trials and concentrate on the last sample. The frontal lobe patients were found impaired in this task.

Corsi later discovered that these patients were impaired in their memory for the ordering of the events. The task Corsi used was to present the subjects with cards that had pairs of pictures or words on them. Occasionally a card was presented with a question mark between the pair. At that point the subject had to tell which of the pictures he had seen more recently. If one of the stimuli is one that has never been seen, then this is a simple recognition task. If both are seen before, then this task requires a comparison of recency. Patients with left temporal lesions are impaired in recognition. The frontal lobe patients intact in recognition but impaired in the recency task.

Moskovitch and Milner tested the frontal lobe patients for release from proactive interference. The task was recall of word lists. Four sets of 12 words of the same category followed by a set of 12 words from a different category are presented. Normal subjects decrease their performance from set 1 to set 4 due to interference. Typically they do as good as the first set in their fifth set. Frontal lobe patients did not get much better in their fifth set. Similar results were observed in Korsakoff's patients but not in temporal lobe patients.

Kolb and Milner discovered deficits in movement copying. An example task was to copy a series of three discrete facial expressions. The frontal lobe patients were observed to make intrusion and omission errors. Part of this impairment might be due to short term memory deficits.

Cortical injuries in the other parts of the brain occasionally cause specific long-term memory difficulties. These deficits are typically very selective and limited to a particular domain. Examples include color amnesia, prosopagnosia (face amnesia), object anomia (inability to remember names of objects), topographical amnesia (inability to remember locations of objects).

Other cortical lesions may also cause short term memory deficits. Warrington and Weiskrantz studied several cases of short term memory deficit. Most likely areas to cause short term memory disorders are the polymodal sensory areas of the posterior parietal cortex, posterior temporal cortex, and the frontal lobes. Short term memory deficits specific to verbal or visual stimuli have been observed. These results imply that STM and LTM are parallel processes and material is processed separately by both.

Korsakoff's disease is another source of severe amnesia. It is seen in chronic alcoholics and thought to be due to lack of vitamin B1. The disease results in degeneration of medial thalamus, mamillary bodies and generalized cerebral atrophy. Symptoms appear within a few days. Sanders and Warrington describe six major symptoms in their seminal paper on Korsakoff [Sanders and Warrington, 1971]. Anterograde amnesia, general retrograde amnesia (unlike temporal lobe patients), confabulation (making up plausible stories for past events), lack of insight (they are typically unaware of their defect), and apathy. Most of these symptoms are clearly in contrast with temporal lobe patients like H. M. Temporal lobe patients show normal release from interference, frontal lobe patients and Korsakoff patients do not. Korsakoff's patients have extensive loss of past memories before the damage, temporal lobe patients do not. Moskovitch suggests that Korsakoff's syndrome is accompanied by frontal lobe deterioration. Korsakoff's patients have normal IQs and other cognitive capabilities are intact in general.

5 Architecture

The ultimate purpose of studying the cellular mechanisms and reviewing behavioral observations is to come up with a functional description of the architecture that supports memory. Unfortunately progress at this front is rather slow. The independent findings are yet to be combined with a model of how things work together. However, in this section, I will review the current findings about the architecture of memory.

Fuster and Jervey showed that temporal lobe structures that are involved in encoding visual information during perception are also involved in storing that information
[Fuster and Jervey, 1982]. This clearly suggests that different types of information are stored differently. If perceptual structures also serve to store information, properties of memory function must be understood within the context of the perceptual function. Specifically they recorded single unit activity with microelectrodes in macaque monkeys performing a visual delayed matching-to-sample task. During the delay, a substantial contingent of cells showed increased, sustained, and in some cases, color-dependent discharge. Fuster and Jervey propose that these cells are engaged in temporary retention of the sample stimulus.

Miyashita and Chang performed a similar study using complex visual stimuli
[Miyashita and Chang, 1988]. They found a group of shape-selective neurons in an anterior ventral part of the temporal cortex of monkeys that exhibit sustained activity during the delay period of a visual short term memory task. They observed that the activity was highly selective for the pictorial information to be memorized and was independent of the physical attributes such as size, orientation, color, or position of the object. These observations suggest that the delay activity represents the short-term memory of the categorized percept of a picture. Another evidence for the storage of visual memory traces in the temporal lobes is that electric stimulation of this area in humans result in recall of imagery.

Gnadt and Andersen showed that memory representations used to guide eye movements are represented at least in part in posterior parietal cortical areas that are used in motor control [Gnadt and Andersen, 1988]. They performed studies in the rhesus monkey during tasks which required saccadic eye movements to remembered target locations in the dark. Neurons in the lateral bank of the intraparietal cortex were found which remained active during the time period for which the monkey had to withhold eye movements while remembering desired target locations. The activity of the cells was tuned for eye movements of specific direction and amplitude, and it was not necessary for a visual stimulus to fall within the response field. The study suggests that the activity of these neurons represent the intent to make eye movements of specific direction and magnitude.

Funahashi and colleagues showed that the dorsolateral prefrontal area (Area 46) contains a structure that codes the spatial locations of stimuli [Funahashi et al., 1989]. This area is very close to the frontal eye fields (Area 8), which play a critical role in planned sequences of eye movements. The area Funahashi studied is spatially organized and has precise connections to the regions of the parietal lobe studied by Gnadt and Andersen. These two studies might be uncovering a combined front-parietal system that codes the locations of the objects and directs eye movements to selected locations.

The studies mentioned so far all focus on the short term memory and stress the fact that the areas of the brain that do the processing also do the storing of information. The long term memory, however, is a different story. The data from disorders indicate several candidate regions of the brain as related to general memory processes. These are anterior temporal cortex, the medial temporal region, medial thalamus, mamillary bodies, and basal forebrain. The interactions between these regions are still speculative. However several models have started to emerge from animal and human studies.

Mishkin outlined the architecture of an entire memory system based on findings from animal studies [Mishkin, 1982]. He theorized about the possible role of the hippocampus and related structures in a model of interacting components. Mishkin postulates that coded representations of stimuli are stored in the higher-order sensory areas of the cortex whenever stimulus activation of these areas also triggers a cortico-limbo-thalamo-cortical circuit. He proposed that the role of this circuit could be either imprinting or rehearsal of the stimuli. The representation stored in the cortex is used for three distinct tasks: recognition, which occurs when the stored representation is reactivated via the original sensory pathway; recall, when it is reactivated via any other pathway; and association, when it activates other stored representations via the outputs of the higher order sensory areas to the relevant structures.

Squire revised Mishkin's model based on the more recent evidence that emphasizes the role of the entorhinal and related cortex and de-emphasizes the role of the amygdala [Squire, 1989]. The entorhinal cortex is the gateway to the hippocampus, and receives input from all of the perceptual systems. Many of its neurons respond selectively to stimuli in multiple sensory modalities. Thus architecturally it has a unique location that would support combining inputs from various sensory modalities. Studies have shown that removal of hippocampus and medial temporal cortex produced severe amnesia, even if the amygdala is preserved.

Another problem with Mishkin's model is that it does not have a clear explanation of how the consolidation process works. Thus it is vague on the question of retrograde amnesia. In an experiment by Sutherland and Arnold, rats were trained to find a hidden location in the Morris Water Task [Sutherland and Arnold, 1987]. The animals were then kept in their cages for 1, 4, 8 or 12 weeks before producing hippocampal damage in different groups. All groups were tested two weeks after the surgery. The finding was that the longer the period between learning and hippocampal damage, the better the performance. This experiment suggests that hippocampus is transiently involved in the memory storage process and that other structures maintain the permanent memories.

Recent work by Wilson and McNaughton hints at interesting possibilities for the role of the hippocampus in consolidation [Wilson and McNaughton, 1994]. They developed a technique by which they can record simultaneously from about a hundred neurons in a rat hippocampus. Their recordings as the rat traversed a new environment confirmed the existence of cells in the hippocampus that are sensitive to particular locations in the environment regardless of orientation or other sensory stimuli. The more interesting observation was the recordings made during the slow-wave sleep preceding and following the behavior. Cells that fired together when the animal occupied particular locations in the environment exhibited an increased tendency to fire together during subsequent sleep, in comparison to sleep episodes preceding the behavioral tasks. Cells that were inactive during behavior, or that were active but had non-overlapping spatial firing, did not show this increase. This suggests that information acquired during active behavior may be re-expressed in hippocampal circuits during sleep, possibly supporting memory consolidation.

It is interesting to note the rapid evolution of the role assigned to the hippocampus in the last half a century [Swanson, 1983]. The first hypothesis was the notion that the hippocampus has a primarily olfactory function. It was called the rhinencephalon or "smell brain". In 1947 Brodal demolished this view by pointing out that conditioned olfactory behavior was not effected by hippocampal ablations, and several anosmotic mammals the hippocampus is well developed. In 1937 Papez proposed based on anatomical evidence that the circuit interrelating the hippocampus, the mammillary body, the anterior thalamic nuclei and the cingulate gyrus could be the basis for emotional behavior. In 1952, MacLean proposed the term "limbic system" to refer to this complex of structures and the related circuitry. He later elaborated by suggesting that there is a basic dichotomy between the "old" (limbic) and the "new" cortex, the former supporting emotional (what we feel) and the latter supporting the cognitive (what we know) functions. The third major hypothesis was prompted by Scoville and Milner's description of patient H. M. in 1957. A large body of animal research since then showed that hippocampal ablations interfere with a variety of learning and memory tasks, that hippocampus contains place units (Hebb's cognitive map of the external world), and it was involved primarily in learning tasks that rely heavily on spatial cues. [O'Keefe and Nadel, 1978].

A more recent review by Eichenbaum and colleagues [Eichenbaum et al., 1992], addresses four questions about the hippocampus: What is the fundamental nature of memory supported by the hippocampal system, what is the contribution of the hippocampus itself among closely related structures to memory, how is information encoded by the activity of hippocampal neurons, and does hippocampus actually store memories. It is pointed out that across species and across learning materials the hippocampal system is critical to declarative memory. This kind of memory differs from hippocampal-independent type by its relational representation and representational flexibility. It is evident that hippocampus itself is one component in a large circuit that includes Ammon's horn, the dentate gyrus, the subiculum, and other areas. Hippocampus receives inputs from several functionally distinct brain areas. Thus the neural activity in the hippocampus presumably reflects all types of sensory and behavioral events, and in particular the relationship between those events. They seem to process properties of stimulus events related to their functional significance, in particular, neuronal activity does not depend on the presence of any particular component of the items they represent. It is also known that hippocampal neurons act as members of a distributed network, and their ensemble activity supports the memories. The hippocampus itself does not store memories permanently, although it keeps them for some variable time after the learning event. It probably functions as an enabler of memory storage in neocortical storage sites.

6 Conclusion

The anatomical evidence from humans is still insufficient. Nevertheless a picture of interlocked systems have started to emerge that support human memory function. The following account from Eichenbaum summarizes the current state of this picture:

> When a relevant stimulus gains one's attention, the hippocampal Θ rhythm [1] is generated. The cellular mechanisms reflected in this rhythm effectively time-lock the arrival of multiple channels of exteroceptive sensory input with behaviorally generated events whose various functional representations in associational cortices converge on the hippocampal network. The overlapping inputs to hippocampal cells within the competitive networks of the hippocampal circuitry shape the configurations of events encoded by individual units, and distribute the representation across these units. The plastic properties of hippocampal physiology, primed by the synchronization reflected in the Θ rhythm, support altered excitability states in cells maximally activated by these events. These cellular changes occur very rapidly, and immediately support a memory at sufficient strength to permit later reoccurrences of even a partial pattern of these events to reactivate the entire network. Furthermore, to the extent that new events share features with items stored previously, these representations are also reactivated and their activity interacts with the representation and storage of current events. Out of the interactions of current and stored representations in the hippocampal network emerges a "memory space," encoding and updating representations of significant relations among new items and all other related items still excitable by hippocampal activity. Such instantiations and reinstantiations occur repetitively over a period of time, reexciting and possibly modifying long-term neocortical representations, enabling memory consolidation. Furthermore, such relational processing permits the same representations to be activated in different (including entirely novel) contexts. The manipulation of information as a consequence of the activation of this flexible representation may indeed constitute the neurobiological embodiment of conscious recollection; certainly flexible representations are required to support conscious recollection and awareness of previous experiences. While the precise processes underlying these putative steps in hippocampal processing and their linkage remain to be demonstrated, and indeed many other questions concerning the functional role of the hippocampus remain to be answered, the details of hippocampal memory processing and hippocampal-dependent memory representation are becoming ever more clear.

[1] A pronounced rhythm that dominates both EEG and unit activity throughout the nonprimate mammalian limbic system during exploratory activity, including that associated with learning. In hippocampus, the Θ rhythm coincides with a cycle of neuronal excitability suggesting that hippocampal processing may occur in discrete processing periods akin to clock cycles in digital computers.

References

[Alvarez and Squire, 1994] Alvarez, P. and Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: A simple network model. In *Proc. Natl. Acad. Sci. USA*, volume 91, pages 7041–7045.

[Ambros-Ingerson et al., 1990] Ambros-Ingerson, J., Granger, R., and Lynch, G. (1990). Simulation of paleocortex performs hierarchical clustering. *Science*, 247:1344–1348.

[Bartlett, 1932] Bartlett, F. C. (1932). *Remembering.* Cambridge University Press.

[Barto and Jordan, 1987] Barto, A. G. and Jordan, M. I. (1987). Gradient following without backpropagation in layered networks. In *Proceedings of the IEEE First Annual International Conference on Neural Networks*, volume 2, pages 629–636.

[Bekkers and Stevens, 1990] Bekkers, J. M. and Stevens, C. F. (1990). Presynaptic mechanism for long-term potentiation in the hippocampus. *Nature*, 346:724–729.

[Bliss and Lomo, 1973] Bliss, T. V. P. and Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, 232:331–356.

[Broadbent, 1958] Broadbent, D. E. (1958). *Perception and communication.* Pergamon.

[Broca, 1861] Broca, P. (1861). Remarques sur le siege de la faculte du langage articule, suivies d'une observation d'aphemie. *Bulletin de la Societe d'anthropologie*, 6:330–357.

[Buckner, 1995] Buckner, R. L. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience*, 15:12–29.

[Carpenter, 1874] Carpenter, W. B. (1874). *Principles of mental physiology.* John Churchill.

[Cohen and Corkin, 1981] Cohen, N. J. and Corkin, S. (1981). The amnesic patient h. m.: Learning and retention of a cognitive skill. *Neuroscience Abstracts*, 7(235).

[Corkin, 1968] Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia*, 6:255–265.

[Corkin, 1984] Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in h. m. *Seminars in Neurology*, 4:249–259.

[de Biran, 1804] de Biran, M. (1804). *The influence of habit on the faculty of thinking.* Williams & Wilkins.

[Edelman et al., 1985] Edelman, G. M., Milner, B., Schank, R. C., Simon, H. A., Dennett, D., and Peacocke, A. (1985). How we know. In Shafto, M., editor, *Nobel Conference XX, Gustavus Adolphus College, St. Peter, Minnesota.* Harper & Row, Washington, D. C.

[Eichenbaum and Cohen, 1988] Eichenbaum, H. and Cohen, N. J. (1988). Representation in the hippocampus:what do hippocampal neurons code? *TINS*, 11(6).

[Eichenbaum et al., 1992] Eichenbaum, H., Otto, T., and Cohen, N. J. (1992). The hippocampus–what does it do? *Behavioral and Neural Biology*, 57:2–36.

[Eichenbaum et al., 1994] Eichenbaum, H., Otto, T., and Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences*, 17:449–518.

[Freud, 1900] Freud, S. (1900). *Interpretation of dreams.* Avon.

[Funahashi et al., 1989] Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the money's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, 61:331–349.

[Fuster and Jervey, 1982] Fuster, J. M. and Jervey, J. P. (1982). Neuronal firing in the inferotemporal cortex of the monkey in a visual memory task. *Journal of Neuroscience*, 2:361–375.

[Gall, 1835] Gall, F. J. (1835). *The influence of the brain on the form of the head.* Marsh, Capen & Lion.

[Gluck and Thompson, 1987] Gluck, M. A. and Thompson, R. F. (1987). Modeling the neural substrates of associative learning and memory: A computational approach. *Psychological Review*, 94:176–191.

[Gnadt and Andersen, 1988] Gnadt, J. W. and Andersen, R. A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. *Experimental Brain Research*, 70:216–220.

[Greenough and Chang, 1985] Greenough, W. T. and Chang, F. F. (1985). Synaptic structural correlates of information storage in mammalian nervous systems. In Cotman, C. W., editor, *Synaptic plasticity.* Guilford Press.

[Hawkins and Kandel, 1984] Hawkins, R. D. and Kandel, E. R. (1984). Is there a cell-biological alphabet for simple forms of learning? *Psychological Review*, 91:375–391.

[Hebb, 1949] Hebb, D. O. (1949). *Organization of behavior.* John Wiley.

[Hering, 1920] Hering, E. (1920). Memory as a universal function of organized matter. In Butler, S., editor, *Unconscious Memory.* Jonathan Cape.

[James, 1890] James, W. (1890). *The principles of psychology.* Henry Holt.

[Kandel, 1991] Kandel, E. R. (1991). Cellular mechanisms of learning and the biological basis of individuality. In Kandel, E. R., Schwartz, J. H., and Jessell, T. M., editors, *Principles of Neural Science*, chapter 65, pages 1009–1031. Appleton & Lange, Norwalk, CT, third edition.

[Kolb and Whishaw, 1990a] Kolb, B. and Whishaw, I. Q. (1990a). *Fundamentals of Human Neuropsychology*, chapter 21. Memory, pages 525–567. W. H. Freeman and Company, third edition.

[Kolb and Whishaw, 1990b] Kolb, B. and Whishaw, I. Q. (1990b). *Fundamentals of Human Neuropsychology*, chapter 24. Spatial Behavior, pages 643–676. W. H. Freeman and Company, third edition.

[Kupfermann, 1991a] Kupfermann, I. (1991a). Learning and memory. In Kandel, E. R., Schwartz, J. H., and Jessell, T. M., editors, *Principles of Neural Science*, chapter 64, pages 997–1008. Appleton & Lange, Norwalk, CT, third edition.

[Kupfermann, 1991b] Kupfermann, I. (1991b). Localization of higher cognitive and affective functions: The association cortices. In Kandel, E. R., Schwartz, J. H., and Jessell, T. M., editors, *Principles of Neural Science*, chapter 53, pages 823–838. Appleton & Lange, Norwalk, CT, third edition.

[Lashley, 1950] Lashley, K. D. (1950). In search of the engram. *Symposia of the Society for Experimental Biology*, 4:454–482.

[Mandler, 1968] Mandler, G. (1968). Association and organization: Facts, fancies, and theories. In Dixon, T. R. and Horton, D. L., editors, *Verbal behavior and general behavior theory*. Englewood Cliffs.

[Marr, 1982] Marr, D. (1982). *Vision*. W. H. Freeman Co.

[Miller, 1956] Miller, G. A. (1956). The magical number seven plus or minus two: Some limits on your capacity for processing information. *Psychological Review*, 63:81–96.

[Milner, 1968] Milner, B. (1968). Disorders of memory after brain lesions in man. *Neuropsychologia*, 6:175–179.

[Milner, 1970] Milner, B. (1970). Memory and the medial temporal regions of the brain. In Probram, K. H. and Broadbent, D. E., editors, *Biology of Memory*. Academic Press.

[Mishkin, 1982] Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society of London*, B 298:85–95.

[Mishkin et al., 1984] Mishkin, M., Malamut, B., and Bachevalier, J. (1984). Memories and habits: Two neural systems. In Lynch, G., McGaugh, J. L., and Weinberger, N. W., editors, *Neurobiology of Learning and Memory*, pages 65–77. Guilford, New York.

[Mishkin and Murray, 1994] Mishkin, M. and Murray, E. A. (1994). Stimulus recognition. *Current Opinion in Neurobiology*, 4:200–206.

[Miyashita and Chang, 1988] Miyashita, Y. and Chang, H. S. (1988). Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature*, 331:68–70.

[Murray et al., 1993] Murray, E. A., Gaffan, D., and Mishkin, M. (1993). Neural substrates of visual stimulus-stimulus association in rhesus monkeys. *Journal of Neuroscience*, 13:4549–4561.

[O'Keefe and Nadel, 1978] O'Keefe, J. and Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford University Press.

[Petrides, 1994] Petrides, M. (1994). Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In *Handbook of Neuropsychology*, volume 9, pages 59–82.

[Pinel, 1992] Pinel, J. P. J. (1992). *Biopsychology*, chapter 14 and 15, pages 457–535. Allyn & Bacon, second edition.

[Potter, 1990] Potter, M. C. (1990). Remembering. In Osherson, D. N. and Smith, E. E., editors, *Thinking*, number 3 in An Invitation to Cognitive Science, pages 332–361. MIT Press, Cambridge, MA.

[Sanders and Warrington, 1971] Sanders, H. I. and Warrington, E. K. (1971). Memory for remote events in amnesic patients. *Brain*, 94:661–668.

[Schacter, 1987] Schacter, D. L. (1987). Implicit memory: History and current status. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 13:501–518.

[Schacter, 1989] Schacter, D. L. (1989). Memory. In Posner, M. I., editor, *Foundations of Cognitive Science*, pages 683–725. MIT Press, Cambridge, MA.

[Schacter and Tulving, 1994] Schacter, D. L. and Tulving, E., editors (1994). *Memory Systems 1994*. MIT Press, Cambridge, MA.

[Shimamura, 1993] Shimamura, A. P. (1993). *Implicit memory: new directions in cognition, development, and neuropsychology*, chapter 12. Neuropsychological analyses of implicit memory: history, methodology and theoretical interpretations. Lawrence Erlbaum, Hillsdale, NJ.

[Shimamura et al., 1987] Shimamura, A. P., Salmon, D. P., Squire, L. R., and Butters, N. (1987). Memory dysfunction and word priming in dementia and amnesia. *Behavioral Neuroscience*, 101:347–351.

[Sperling, 1960] Sperling, G. (1960). The information available in brief visual presentations. *Psychological Monographs*, 74(498).

[Spurzheim, 1834] Spurzheim, J. G. (1834). *Phrenology: The doctrine of mental phenomena*. Marsh, Capen & Lion.

[Squire, 1989] Squire, L. R. (1989). Mechanisms of memory. In Kelner, K. L. and Koshland, D. E., editors, *Molecules to Models: Advances in Neuroscience*. American Association for the Advancement of Science, Washington, D. C.

[Squire, 1992] Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, 99:195–231.

[Sutherland and Arnold, 1987] Sutherland, R. J. and Arnold, K. (1987). Temporally graded loss of memory after hippocampal damage. *Neuroscience*, 22.

[Swanson, 1983] Swanson, L. W. (1983). The hippocampus and the concept of the limbic system. In Seifert, W., editor, *Neurobiology of the hippocampus*, pages 3–19. Academic Press.

[Tulving, 1962] Tulving, E. (1962). Subjective organization in free recall of unrelated words. *Psychological Review*, 69:344–354.

[Wilson and McNaughton, 1993] Wilson, M. A. and McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. *Science*, 261:1055–1058.

[Wilson and McNaughton, 1994] Wilson, M. A. and McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, 265:676–679.