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Nervous System

See **Autonomic Nervous System**

Neural Activity

See **Decoding Neural Population Activity; Decoding Single Neuron Activity; Diffusion Models and Neural Activity; Rate versus Temporal Coding Models; Single Neuron Recording**

Neural Basis of Memory: Systems Level

Introductory article

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A systems level approach to the neuroscientific investigation of memory looks at the ways in which different areas of the brain interact and communicate to achieve this function.

INTRODUCTION

What did you eat for dinner two days ago? What is the name of the mouse in the story *Dumbo*? How many turns do you need to make to get

from your front door to your bedroom? How are you able to understand the visual symbols in this sentence? Memory – our remarkable capacity to learn and retain information – offers the answers to these questions. Across a lifetime, we encounter, store and retrieve an enormous amount of information. We have knowledge about ourselves, about world facts, and even about things that we do not usually associate with our memory, such as habits and skills. How does

the brain accomplish such extraordinary feats of memory?

The study of memory has been approached from many scientific disciplines. Neurobiological approaches address the microstructure of memory, such as the biochemical mechanisms within neurons or the formation of synaptic connections between neurons. Such processes allow the brain to adapt to changes in the environment. At a more global level of analysis, or what is often described as a systems level, neuroscientists describe how brain regions interact and communicate to serve human memory. Take, by analogy, the levels at which one could understand how an automobile works: at a microscopic level, one could study how the fuel molecules, through combustion, react to make an automobile move, whereas at the systems level, one could study the function of specific components, such as the engine or the transmission, and then determine how these components work together. This article approaches human memory from a systems level, focusing on brain regions that contribute to various components of human memory.

Our understanding of human memory has been significantly advanced by integrating neuroscience with cognitive science – a field of research called cognitive neuroscience. Over the past century medical scientists have studied patients with brain injury as a way to understand the biology of human memory. Around 1970, cognitive scientists became interested in neuropsychological studies, because such studies often demonstrated modularity in cognitive function. For example, brain injury could severely impair an aspect of memory, but leave intact other cognition functions such as attention, language, and problem-solving skills. More recently, studies using neuroimaging techniques – such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) – have led to finer analyses concerning the relationship between brain regions and memory function. In such studies, it is possible to show that specific brain regions become active when individuals engage in memory processes, such as learning a list of words or trying to remember a past event. The following sections will identify components of memory from a cognitive neuroscience perspective.

ORGANIC AMNESIA AND THE MEDIAL TEMPORAL CORTEX

A significant advance in understanding the biology of human memory occurred by chance through the

study of a now-famous neurological patient known by his initials, HM. This patient underwent an experimental surgical procedure in 1953 to relieve severe epilepsy. The surgery involved removal of brain tissue in the medial temporal cortex, a region of the cerebral cortex that encompasses the inner (medial) surface of the temporal lobe. The operation included removal of the hippocampus, a brain structure adjacent to the cerebral cortex. Following surgery, HM's epileptic seizures were reduced, but he was left with a profound organic amnesia – that is, he was unable to remember events and information encountered since his operation. For example, when HM was asked what he had had for lunch half an hour previously, he could not remember what he had eaten, or even if he had eaten at all. Despite this severe memory impairment, there was little impairment in intellectual ability or language skills. Indeed, HM had a normal IQ (intelligence quotient) and could communicate fluently with others. There was some memory impairment for information that occurred before his operation, a disorder called retrograde amnesia. For example, HM could not recall the layout of the hospital in which he was treated, or recall the death of a favorite uncle who had died three years previously. Yet HM's retrograde amnesia was not gross, as indicated by the fact that he performed as well as others on a face recognition test of celebrities who became famous prior to his operation. Also, he was capable of recollecting events and episodes from his childhood.

Clinical observations indicate that HM's memory for ongoing events is still severely impaired. He is somewhat aware of his condition, as indicated by the following quote:

Right now, I'm wondering. Have I done or said something amiss? You see, at this moment everything looks clear to me, but what happened just before? That's what worries me. It's like waking from a dream; I just don't know. It's like waking from a dream.

Indeed, HM lacks the ability to acquire and retain events and facts encountered since his operation. The impairment affects information received from all types of sensory receptor and includes impairment of both verbal and nonverbal (e.g. spatial) memory. For example, HM has failed to add to his vocabulary new words such as 'jacuzzi', because such words have been added to the language since his surgery. He also exhibits severe impairment on laboratory tests in which he is asked to recall or recognize recently presented words and pictures.

Studies of neurological disorders that affect the medial temporal cortex have confirmed the

importance of this brain region for memory. For example, tumors or strokes occurring in the medial temporal cortex can cause organic amnesia. Also, other neurological disorders – such as viral infections, ischemia (loss of blood flow to the brain) or hypoxia (loss of oxygen to the brain) – particularly damage the medial temporal cortex. In these cases, the inability to retain newly learned information is the outstanding cognitive disorder. Finally, in Alzheimer disease, organic amnesia is usually the most significant impairment in the early stages. However, this is a degenerative disease, and as more brain areas become affected more cognitive functions become disrupted.

Events in your life consist of a variety of psychological experiences, such as sensory inputs, ideas, feelings, and actions. Indeed, every moment is completely unique in that these experiences – perceptions, thoughts, emotions, actions – will happen together only once. If something significant occurs at any particular moment, such as a life-threatening or life-enriching event, it would be useful to be able to bind or associate the varied aspects of the event as one encapsulated ‘episodic’ memory. Likewise, if you are asked to take an examination, say a history test, it is important to be able to relate or associate a diverse set of facts into an encapsulated ‘semantic’ or conceptual memory. To form such encapsulated memories, it is important to relate quickly many aspects of an event or concept.

A prominent view of medial temporal function is that it allows for the rapid linking of these experiences, sometimes called ‘relational binding’. The medial temporal cortex is ideally situated for such relational binding to occur. Many parts of the cerebral cortex extend neural projections that converge onto regions within the medial temporal cortex, from which neural projections extend back to these cortical areas. It is believed that the medial temporal cortex enables neural activations in any given moment to be bound as an encapsulated set of associations. Without this ability, memory would dissolve into fragments unattached or unrelated to any particular time, place, or concept.

WORKING MEMORY AND THE PREFRONTAL CORTEX

Despite HM’s amnesic disorder, he is able to think, communicate, and even retrieve childhood memories. In addition, he has the capacity to keep information in mind for brief periods: for example, he can hold in mind a short series of digits, such as a

telephone number. Yet, as soon he is distracted, the information is lost. These findings suggest that organic amnesia does not affect the online processing of information, or what psychologists call ‘working memory’. Working memory refers to the processes that allow us to keep information in mind. These processes include the ability to select, retrieve, and maintain information in a short-term or transient manner. With respect to the example of holding a telephone number in mind, working memory is essential when it is necessary to maintain or use information after it has been presented. Animal studies have been invaluable in defining a brain region – the prefrontal cortex – that is essential for working memory. In such studies, neurons in the prefrontal cortex are activated when an animal must maintain information, such as the location of a food item after it has been hidden. Moreover, when this brain region is damaged, the ability to maintain information is disrupted.

The prefrontal cortex is part of the most anterior section of the frontal lobes. It is a large area, comprising 28 percent of the human cortex. Disruption of working memory is apparent in people with damage to the prefrontal cortex. Such individuals have difficulty paying attention and keeping things in mind. For example, people with frontal lobe lesions exhibit severe deficits in the ability to keep in mind a series of items, such as digits (telephone numbers), sounds or spatial locations. In neuroimaging studies using PET and fMRI, increased activation in prefrontal cortex occurs when individuals are asked to keep information in mind. The left prefrontal cortex is involved in holding verbal information whereas the right prefrontal cortex is involved in holding spatial information.

Working memory is important for efficient learning and retrieval. For example, try to learn the following series of words: sister, soda, milk, shoe, father, pants, juice, brother, hat. Maybe you used a strategy to help you organize the words. Perhaps you noticed that the words could be encoded or grouped into three meaningful categories: family relatives, drinks, and clothing. Learning is significantly benefited by the meaningful organization of information. Making new information meaningful to you enhances the integration of new information into your existing database. This strategy involves working memory, because it is necessary to manipulate and update the information in mind. That is, the more you think about the information and why it is meaningful to you, the more you actively integrate the new information with what you already know. Individuals with prefrontal

damage exhibit problems in organizing their thoughts and memories. These people do not develop learning strategies or think deeply about what they need to learn. For example, they do not group words into meaningful categories. In neuroimaging studies, the prefrontal cortex is particularly active when individuals are asked to consider the meaning of words. Also, prefrontal activation during the learning of words is greater for words that are later remembered than for words that are forgotten. This finding shows that activity in the prefrontal cortex during learning increases the chances of retrieving the information at a later time.

Working memory is also important in retrieving information. Consider a fairly simple memory retrieval task – try to retrieve as many animals that you can think of in 60s. This task requires you to search your memories and retrieve specific items. Perhaps you developed a strategy, such as retrieving animals within certain categories, such as pets, farm animals and animals one sees at the zoo, or maybe you went down the alphabet and used each letter as a cue to retrieve animal names. Such strategies are efficient because they facilitate the retrieval of different items and prevent repeating the same ones. Keeping track of which animals were already elicited requires you to keep in mind the animals and update this list each time you retrieve an item. Individuals with prefrontal damage have difficulty keeping track of previously retrieved items. It is as if these items get in the way, making it harder to retrieve others. Thus, these people report only four or five different animals in a minute and often repeat the same ones over and over. Neuroimaging studies have corroborated the importance of the prefrontal cortex during memory retrieval: when brain activity is measured while individuals are asked to retrieve information, the prefrontal cortex is particularly active.

Findings from studies of patients with prefrontal damage and findings from neuroimaging studies suggest that the prefrontal cortex enables efficient organization of information in mind. That is, when one is working with memories, it is necessary to select relevant information, update that information, and use it to respond. Cognitive scientists use the term ‘executive control’ to characterize the processes associated with the selection, control, and manipulation of information in working memory. Related issues include selective attention and response supervision. Selecting and using information in working memory is essential for efficient processing in many cognitive domains. Indeed, the prefrontal cortex, which is most closely tied to executive control, appears to be involved not only

in the control of memory, but also in the selection of perceptual features, thinking, problem-solving, and response selection. Different areas of the prefrontal cortex appear to be responsible for the control of different aspects of information processing.

REPRESENTING KNOWLEDGE AND PAST EXPERIENCES

So far, we have looked at how the medial temporal cortex binds experiences together to form new memories and how the prefrontal cortex monitors and controls memory activations. But what actually is stored in memory? This intriguing question has bemused scientists, philosophers and poets. Karl Lashley, the noted neuroscientist, argued that there was not a single location where a particular memory was stored. Instead, memories were distributed widely in the brain. To demonstrate this notion, Lashley trained rats to follow a particular pathway in a maze in order to obtain food. Lashley found that lesions of many brain regions, not just one region, impaired performance on this task; moreover, the severity of impairment was determined by the size of the lesion rather than its location. This idea – that memories were distributed in many parts of the brain – countered ‘filing cabinet’ views of memory in which specific memories were localized in specific areas in the brain.

Today, most cognitive neuroscientists take a middle-of-the-road position between distributed and localized views of memory storage. It is not likely that any memory, such as memory of a past birthday party or your knowledge about a particular historical event, is stored in a small, localized area in your brain. Indeed, there is no evidence that a brain injury would produce an absence of a specific piece of information in one’s memory, which would be akin to throwing out a specific folder in your filing cabinet. Thus, memory storage appears to be distributed or represented in many parts of the brain. However, certain features of a memory, such as memory for faces, can be disrupted by specific brain damage. In many cases, these aspects are tied to the way the brain uses or processes such information. Thus, although memories may be distributed widely in the brain, each area may contribute to the memory in a different way. For instance, memories of the sights, sounds, feelings, and actions experienced during a birthday party are likely to be stored in different parts of your brain. When you recollect such past events, you draw on many of these different aspects of your memory, not just any localized one.

Episodic and Semantic Memory

Episodic memory refers to memories that are tied to one's autobiography. These memories are embedded within a context of time and place. Semantic memory refers to the vast database of factual knowledge stored in memory. Such knowledge is usually learned on many occasions and thus not tied to any specific time in one's life. For example, your knowledge of how memory works comes from many experiences (hopefully one of which is from reading this text). The distinction between episodic and semantic memory was first developed by Endel Tulving in 1973. It has been useful in denoting two major divisions of memory representation.

There are both similarities and differences in the manner in which episodic and semantic memory are represented in the brain. One similarity is that the acquisition of new episodic and semantic memory is dependent upon the integrity of the medial temporal cortex. That is, people with organic amnesia have difficulty remembering autobiographical events experienced since the onset of amnesia as well as learning new factual information. Indeed, the outstanding feature of organic amnesia is a deficit in forming new episodic memory. However, these people also fail to learn new semantic knowledge. As mentioned earlier, HM has no knowledge of words that entered his culture after the onset of his amnesia. In another example, a patient with amnesia had been vice-president of an optical firm and was very knowledgeable about the field of optics. However, when he became amnesic, this knowledge did not grow as he was unable to add to this knowledge base. Thus, the acquisition of both episodic and semantic memories depends upon the medial temporal cortex.

One difference between episodic and semantic memory is the extent to which they are represented in the two cerebral hemispheres. It has been known for over a century that the left hemisphere in most individuals is specialized for language processes. Much of our verbal processes and verbal knowledge, such as knowledge about phonology and word definitions, are largely represented in the left cerebral hemisphere. The right hemisphere in most individuals is specialized for spatial processes. For example, damage to the right hemisphere often produces spatial disorders, such as a 'neglect' syndrome in which individuals fail to attend to stimuli on one side. As a large proportion of episodic memory is spatial in nature, damage to the right hemisphere tends to produce greater

disruption of episodic memory than semantic memory. As semantic memory is often more tied to verbal processing, such as factual knowledge read in books, it is often the case that semantic memory is more disrupted by damage to the left cerebral hemisphere. As mentioned earlier, such memories are widely distributed. Thus, extensive damage to one hemisphere is needed to observe disruption in episodic or semantic memory. Moreover, such damage does not appear to reflect a loss of a specific memory, but instead impairment is indicated by diffuse or fuzzy memories.

Category-specific Knowledge

The notion of a widely distributed memory system suggests that memory is multiply represented in many brain regions. This kind of memory representation is efficient because damage to one region may degrade memory but it is unlikely that it will totally abolish it. Yet, as mentioned above, there appear to be features or categories of knowledge that are grouped together. Interestingly, in rare cases of brain injury, there appear to be category-specific deficits of semantic knowledge. That is, some affected individuals exhibit greater problems in recollecting certain features of knowledge than others. One outstanding impairment involves a disorder in remembering faces. This impairment (prosopagnosia) is often caused by damage to ventral-posterior regions of the cerebral cortex; it affects visual recognition of all faces, including the patient's own face. Recent fMRI studies have identified an area within this region, called the fusiform gyrus, that is highly active during the viewing of faces. Although this area is involved in the visual memory of faces, it does not disrupt all memories for people. Patients with prosopagnosia can recognize familiar individuals, such as friends and family, by their voices.

In rare cases, specific loss of a semantic category can occur. For example, a person can exhibit a severe loss in the ability to recognize drawings of common animals, whereas the same individual can recognize drawings of manufactured objects, such as common tools. Interestingly, other affected individuals may exhibit exactly the opposite pattern – an inability to recognize common tools while retaining the ability to name common animals. Such cases suggest that the representations of certain aspects of knowledge are localized in different brain regions. In these people it is difficult to ascertain the brain regions responsible for such category-specific deficits, because it is often the case that the brain injury is large or diffuse.

Do category-specific deficits in semantic knowledge suggest that our memories are stored in a localized rather than a distributed manner? It is unlikely that a specific memory, such as memory of a pet you once owned, is represented in a specific location in the brain. How, then, can one interpret findings of a separation of the concept of animals from that of tools? Neuroimaging studies have shed some light on this issue. In one PET study, participants viewed drawings of animals, tools, or nonsense forms. The nonsense forms were used as control stimuli, and PET activation in response to drawings of animals and tools was compared with activation to these control stimuli. The study showed that both animals and tools activated bilateral areas in the ventral temporal cortex, suggesting that semantic knowledge of animals and tools has broad and overlapping (i.e. distributed) representation.

There were, however, some category-specific activations. Drawings of animals but not tools activated areas in the occipital cortex, an area of the brain associated with visual processing. Drawings of tools but not animals activated premotor areas in the frontal cortex, an area that is also activated during imagined hand movements. Such findings suggest that category-specific knowledge may be tied to the manner in which such information is encoded or used. Animals tend to be encoded and encountered visually, whereas tools are manipulated. It appears that our memories are not stored as purely abstract, semantic representations. Instead, they are associated with the manner in which they have been encoded and used. Apparently, the distribution of our semantic knowledge is related to the distribution of other cognitive processes in the brain, such as visual, auditory, verbal, spatial, emotional, and motor processes.

Procedural Memory: Habits and Skills

The ability to read, drive a car or swim certainly requires memory. This kind of memory, however, is not represented in the same manner as other forms of memory, such as semantic or episodic memory. Skills involve the tuning or coordinating of sensory and motor associations. Procedural memory refers to the processes and representations associated with habits and skilled behavior. Thus, procedural memory is linked specifically to neural circuits associated with the modification of perceptual and motor function. For example, a skilled behavior such as throwing a ball or playing a musical instrument involves the modification and tuning of various perceptual-motor circuits. It is

inherently 'procedural' in that skilled behavior is expressed as a sequence of finely tuned movements. Procedural memory can occur without explicit or conscious knowledge of the training session. Indeed, it is often the case that conscious intervention or feedback can disrupt the expression of skills.

Procedural memory is unique in that it appears to be independent of the medial temporal cortex. One of the most striking findings is that people with amnesia can learn simple skills in an entirely normal fashion. For example, HM showed learning and retention in a mirror-drawing task in which he was required to trace the outline of a star while viewing the star through a mirror. The task is difficult at first but then becomes easier with practice. HM exhibited normal learning and retained this skill over days of practice. Another skill learning task, the pursuit-rotor task, has been used to test people with brain injury. In this task, the patient learns to keep a stylus on a rotating target. In these tests, HM and other amnesic patients perform well, even when tested the next day. However, such patients have no memory of having performed the task before.

Habits or dispositions are forms of procedural memory that can be acquired without conscious awareness. For example, during an interview with an amnesic patient, a neurologist hid a pin between his fingers and surreptitiously pricked the patient on the hand. At a later time during the interview, he once again reached for the patient's hand, but the patient quickly withdrew her hand. The patient did not acknowledge the previous incident, and, when asked why she withdrew her hand, she simply stated, 'Sometimes pins are hidden in people's hands.' This anecdote is an example of stimulus-response habit learning without awareness, or what is called 'fear conditioning'.

Other habitual forms of learning can be demonstrated in studies of Pavlovian classical conditioning, in which a tone is paired with a puff of air to the eye, causing the subject to blink. After several trials, the person will blink on hearing tone by itself. This kind of habit conditioning is normal in individuals with amnesia. These people retained the eyeblink response for as long as 24h, even though they did not recognize the test apparatus.

Such examples of habits and skill learning have been used to study subcomponents of procedural memory, such as timing, sequencing, and storing of perceptual-motor associations. Procedural memory is presumed to involve both cortical and subcortical circuits. At the cortical level, procedural memory is assumed to depend significantly upon unimodal

sensory systems in posterior cortex, and motor and premotor systems in frontal cortex. At the subcortical level, the cerebellum and basal ganglia appear to be significantly involved in skilled behavior.

Functional imaging studies have provided some additional support for the participation of the basal ganglia in motor skill learning. In one study, participants underwent PET scanning while learning a finger-tapping skill. Comparisons between activations seen during initial stages of learning and skilled performance revealed reductions in basal ganglia activation over the course of learning, perhaps reflecting increased processing efficiency. Changes in activation over the course of motor skill learning have also been observed in motor cortex, somatosensory processing areas of thalamus and cortex, and the cerebellum – indeed, in all areas thought to be involved in sensorimotor behavior. These findings suggest that the products of skill learning are represented in widely distributed networks involving many, if not all, of the brain areas that contribute to performance of the skill.

CONCLUSION

Findings from both neurological patients and neuroimaging studies have suggested that certain brain regions contribute to human memory. The medial temporal cortex is essential for the learning of new information. People with organic amnesia following damage to this brain region have difficulty learning new episodic and semantic information. Conceptually, the medial temporal cortex appears to be involved in relational binding, which enables new information to be linked or associated with existing knowledge. The prefrontal cortex is critical for the selection and control of activated memories. The notion of executive control is used to describe the role of the prefrontal cortex in activating memories.

We know less about the manner in which memories are actually stored. Cognitive scientists suggest that memories are stored as a widely distributed network of knowledge. Neuroimaging studies suggest that our memories are not simply abstract concepts but are instead stored with

respect to the way they were encoded and used. Thus, some memories are tied to sensory processes whereas others are tied to motor functions. Moreover, procedural memory appears to be represented in a different manner from episodic or semantic memory. That is, our memory for skills and habits is less available to conscious awareness and appears to be represented as the tuning of associations between sensory and motor functions.

Based on this analysis, cognitive neuroscience provides a useful framework in which to conceptualize the intricacies of human memory. It has been possible to identify components of memory function, such as relational binding, working memory, episodic memory, semantic memory, and procedural memory. Just as one component of an automobile, such as the engine or transmission system, cannot completely define its working, it is impossible to identify one component or region of the brain that completely defines the workings of human memory. It is the interplay of these components that provides us with the rich and seemingly endless experience of memories.

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