

Neuroimaging Studies of Memory

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Some Introductory Concepts

Types of Memory. One of the critical properties that makes the human mind so extraordinarily suited to understanding and dealing with the world is its ability to shift in time—to model the future and reconstruct the past. Reconstructing the past requires memory, and memory is fundamental to nearly any cognitive skill. It is involved in complex processes such as problem-solving, and it is involved in even what seem to be the simplest skills, such as recognizing a familiar face. The role played by memory in cognition is complex enough that not just a single memory system will do. Humans and other animals have several memory systems with different characteristics and different neural implementations, and these systems, acting in concert, contribute to the human mind's tremendous adaptability.

At the broadest level, one can distinguish between "working memory" and "long-term memory." Working memory refers to the system that stores a small amount of information for a brief span of time. Information stored in working memory is then used in the service of other cognitive tasks. For example, if you were solving an arithmetic problem such as $817 + 723$ without the benefit of writing anything on paper, working memory would be used to store the problem, store the intermediate steps in the addition, and store the final solution. In addition to temporary storage, an important component of working memory is what is called "executive processing:" the set of operations that permit one to manipulate the contents of working memory. In the previous example, executive processes would be involved in switching attention from one column of addition to another and in organizing the order of steps to arrive at a final sum. While there is as yet no overall agreement about a full list of executive processes, they can generally be thought of as operations that regulate the processes operating on the contents of working memory, processes such as selective attention to relevant information (more about this shortly).

In contrast to the short duration and small capacity of working memory, long-term memory is a system with very long-duration memory traces and very large storage capacity. In our mental arithmetic example above, long-term memory would be the repository of the facts of addition, which would be needed to solve the mental arithmetic problem. Of course, it stores much more than that. For example, it is the repository of all the words we know in our language; of sensory information that we all have stored for untold numbers of events (e.g., the taste of a

good chocolate); of spatial information we have stored for navigating around our world; and so on. In addition, many pieces of information are stored that we don't normally retrieve consciously, but that nevertheless guide our everyday behavior, such as the rules of language or habitual actions in which we engage every day.

Larry Squire of the University of California and Endel Tulving of the University of Toronto have proposed schemes that summarize the various forms of long-term memory. One way of synthesizing and expanding these schemes is shown in Figure 1. The figure shows that there are two broad divisions of long-term memory: declarative and procedural. Declarative memory refers to the facts and events that we can retrieve at will, often consciously. By contrast, procedural memory refers to stored information that has an impact on our behavior, but that is not willfully retrieved. Consider, for example, the concept of a bicycle. A declarative memory you might have of a bicycle is that it is blue, has 21 gears, mountain-terrain tires, two handbrakes, and so on. These are all facts that can be willfully retrieved from memory. By contrast, you also have stored information that allows you to ride your bicycle—a task that any 6-year old will tell you is not easy. This information is not consciously retrievable; indeed, it is a nontrivial problem in physics and kinesiology to describe just how people are able to ride a two-wheeled bicycle without falling over. The contrast between these two sorts of memory is a contrast between declarative and procedural memory. Perhaps the most compelling evidence that procedural knowledge is different from declarative knowledge is that patients with damage to their hippocampi and surrounding medial temporal lobes can learn new procedural skills, even though they cannot encode where they learned the skill or remember any details of having practiced it, even when that practice occurred very recently. Other patients with cerebellar damage can remember the practice sessions, but their skills on most motor tasks do not improve. This pattern of deficits, called a double dissociation, helps define procedural and declarative processes as distinct types of memory.

Declarative memory itself comes in two forms. One is called episodic memory, or memory for specific events, and it consists of memory traces that are accompanied by memory for the context in which they were formed. Each piece of episodic memory has a source tag associated with it, possibly including the time and place of memory formation and other details about the context. When retrieving an episodic memory, one can retrieve either the item itself given information about the source, or the source, given information about the item. For example, you may recall where and when you

purchased your current bicycle, or given the time and place, you may recall the features of the bicycle that you purchased. The other category of declarative memory is semantic: This type of memory consists of the vast store of facts and events that you have in long-term memory, regardless of whether you can retrieve when and where you learned them. For example, you may remember the fact that bicycles can be mountain bikes, racing bikes, hybrid bikes, and so on, yet you may not be able to recall when or where you learned this semantic fact

Procedural memories also are of various sorts. There are skills, for example, such as riding a bicycle. There are classically conditioned responses, which entail a previous pairing of an unconditioned with a conditioned stimulus to yield a conditioned response. And there are cases of priming, in which a previously learned piece of information facilitates processing of some new piece of information. Psychological measures of priming, such as decreases in response time to recognize a previously viewed word, indicate that a trace of the previously learned piece of information is affecting current cognitive processing—even if there is no conscious recollection of having seen the word before.

Another important dimension of memory, whether working or long-term, is the type of information being stored. As we shall see below, the brain circuitry involved in a memory task honors the type of information that is stored and retrieved. Perhaps the most frequently studied case of this concerns the distinction between linguistic information (such as letters, words, sentences, and stories) and visual or spatial information (such as a scene, an object, a face, or a spatial environment). There is by now ample evidence that the two hemispheres of the brain are differentially activated by these two types of information, with the left hemisphere specialized for verbal information and the right for visual or spatial information in most humans.

Types of processes. Memory entails three cognitive operations: encoding, storage, and retrieval. These terms refer to the sequence in which memory processes are thought to occur. Entering information is first put into the proper internal code and a new memory trace is formed (encoding). Encoding is followed by storage of the information for some period of time. This stage may include consolidation, or alteration of memory traces to make them last longer and be easily retrievable. Retrieval is the process of reporting information from storage.

The nature of encoding depends on two factors: the type of material that is involved in the memory task and the task that is performed with that material. The type of material exerts a strong

influence on the path of activity in the brain early in the processing sequence. The best example of this is the visual system. Spatial information about a visual stimulus is selectively routed to a dorsal stream of information processing that mainly includes the parietal lobes, whereas information about shape and other nonspatial object-features of the same stimulus is processed by a ventral stream in the occipital and inferior temporal lobes. Generalizing from this example, we can say that the nature of incoming information will influence the path of processing that the information takes in the brain. Beyond this, though, there is also an influence of the task with which a person is faced, as many different operations may be performed on any given type of material. For example, one can process a word by noting its meaning or by noting whether it is printed in uppercase or lowercase letters. These very different types of processing on the very same stimulus yield different patterns of activation in the brain, as we shall see below.

Once encoded, information is retained for some period of time. Consistent with the fundamental distinction between working and long-term memory, the length of the retention interval will in large part determine which of these systems is most heavily involved. Retrieval after short retention intervals—up to, perhaps, intervals as long as 30 seconds to one minute—uses working memory. Retrieval of information stored for longer periods will under most circumstances necessitate the involvement of long-term memory storage. Which memory systems is engaged will be revealed by the circuitry that is activated. Working memory engages circuitry in frontal and parietal cortices most prominently, whereas long-term memory requires involvement of frontal and parietal circuitry as well as hippocampal and parahippocampal mechanisms.

Just as encoding different types of material engages different mechanisms, storage of different types of material also requires different mechanisms. This has been demonstrated most handsomely in the contrast between verbal and visual material, which respectively activate left and right hemisphere structures predominantly. This distinction has been demonstrated for both working memory and long-term memory, as we shall see below.

Once encoded and stored, information in memory can then be retrieved as needed. Suppose, for example, that you ask a person to memorize a list of words. Retrieval can be accomplished in several ways. You might simply ask the person to recall as many of the words as possible (free recall). Or you might guide recall by giving some of the words on the list as hints and asking the person to recall the others (cued recall). Or you might present the person with a longer list of words,

some of which were presented on the original list and some not, and the person has to decide which is which (recognition). Any of these procedures requires the person to access the stored information in memory and produce an explicit response that depends on that stored information. For this reason, these are often called explicit tests of memory. However, there are also implicit tests. Suppose, for example, that you presented someone a list of words and later flashed the same words and new words, one by one, so briefly that they were difficult to identify. If your subject were more accurate in identifying words that had been presented on the original list than ones that hadn't (which is what happens in this perceptual identification situation), then one could conclude that the original words were stored in memory even though no explicit retrieval of them was ever demanded. The process of storage and use of information without explicit memory is called priming. Evidence from PET and fMRI suggests that implicit and explicit tests of memory recruit different brain areas, as reviewed below.

With these preliminaries about memory in place, we are now in a position to review what neuroimaging evidence has contributed to understanding basic mechanisms of human memory.

Working Memory

The canonical model of working memory is due originally to Alan Baddeley, and it is this model that has been investigated in detail using neuroimaging methods. The model claims a fundamental distinction between short-term storage of information and executive processes that manipulate this information. This general view is supported by the existence of patients who have intact short-term storage, but deficits in executive processes; this pattern of impairments contrasts with that of other patients who have deficits in executive processing but intact short-term storage. Such a double dissociation suggests that the circuitry of storage and executive processing are separable, and imaging studies have confirmed this separability.

Short-term Storage. The short-term storage of information in working memory appears to be accomplished via two mechanisms: one that retains information and another that "rehearses" that information in order to keep the memory traces active during a retention interval. This is perhaps best illustrated for verbal information. A task that has been used frequently to study the mechanisms of verbal working memory in neuroimaging experiments is the

item-recognition task. In this task, participants are presented a small number of target items, typically randomly selected letters, to store for a retention interval of several seconds. Following this interval, a single probe item is presented and participants must decide whether this item was a member of the memorized set. When participants engage in this task in PET and fMRI settings, there are a number of easily replicable sites of activation compared to a control condition that does not require memory at all or in which the memory requirement is minimal. One frequent site of activation is in posterior parietal cortex, typically more prominently in the left hemisphere than the right. In addition, a set of activations appears in frontal areas, including inferior frontal gyrus on the left, premotor cortex (more prominently on the left than on the right), and supplementary motor cortex. These brain regions, and all other major regions discussed throughout this chapter, are shown in Figure 2.

The frontal cortical areas that are activated in this task are quite similar to those activated in a task that requires making judgments of rhyming, a task that presumably requires producing a speech-like representation. So, it is likely that these frontal areas are ones involved in rehearsal, which involves internally generating and regenerating a speech-like code for the stored verbal material. The posterior parietal sites have been suggested as sites for the storage of verbal information as well as for switching attention between one item and another.

The purported dissociation between the frontal and parietal sites is nicely supported by a study that used a different task involving verbal working memory, the 2-back task. In this task, participants see a series of letters presented at a pace of one every 2.5 seconds, and they must judge for each whether it matches in identity the one that appeared two letters back in the series. This task clearly requires storage and rehearsal of each letter, as well as other processes that we discuss below. Compared to a task in which participants must simply judge whether each letter in the series matches a single target (say, the letter "P"), the 2-back task produces activations in regions similar to the item-recognition task. This is as it should be if both tasks involve storage and rehearsal. Beyond this, though, the 2-back task has also been compared to another condition, one in which participants had to silently rehearse letters to themselves with little storage requirement (e.g., say the letter "P" for 3 seconds, followed by silently saying the letter "M", and so on). Subtraction of the activation in this Rehearsal condition from that in the 2-back condition revealed much lower activation in the frontal areas. The Rehearsal condition is presumed to involve the explicit production of silent speech. Subtracting the activations in this

condition from those in the 2-back condition reduces frontal but not parietal activation; therefore, one can conclude that the frontal activations in the 2-back and other verbal working memory tasks must reflect an inner rehearsal process as part of those tasks. These same frontal regions are also activated in tasks that require a recall response, so they are not unique to the peculiarities of the item-recognition task or the 2-back matching task.

Just as we can identify the frontal sites used in verbal rehearsal, we can also identify the parietal sites used in verbal storage. Evidence that the parietal sites are used in part for storage comes from a study in which subjects memorized a set of nonsense letter strings (e.g., "MAVER"), and then kept these items in memory during a retention interval of some 50 seconds, during which they were PET scanned. After the scan, they had to retrieve the items to be sure that they had been accurately stored. Scanning during just the retention interval allows one to isolate storage processes, or at least to concentrate scanning on storage. One study using this procedure found posterior parietal activations, leading to the conclusion that these activations reflected storage processes, and not encoding or retrieval processes.

Storage and rehearsal should not be restricted to verbal information, of course, if they are general properties of working memory as Baddeley supposed. Indeed, many studies have investigated the storage and rehearsal circuitry used for spatial information as well. The clearest result of these studies is that the circuitry activated by spatial information in a working memory task is quite different from that activated by verbal information, even when the tasks are quite similar and only the material differs. For example, in an analog to the item recognition task, subjects are presented a set of dots on a screen and asked to store their locations in memory. Following a retention interval of several seconds, they are presented with a single probe dot, and their task is to decide whether it appears at the same location as one of the locations they have stored. This task has the same formal structure as the item-recognition task for letters, yet it yields activations that are quite different. In common are activations in posterior parietal and premotor cortex, although with a tendency for greater activation in the right than the left hemisphere. However, quite different are activations in occipital cortex, superior frontal cortex, and inferior frontal cortex, most prominently in the right hemisphere.

The common activations in parietal and premotor cortex between verbal and spatial versions of the task suggest that there are some processes in common between the tasks, possibly having to do in

part with allocating attention to several items in memory. However, the differences in activations suggest that the mechanisms by which information is stored and rehearsed may be different. Indeed, there is evidence of a similarity in circuitry between processes mediating spatial working memory and those mediating shifts of attention to various locations in the visual field when stimuli are being perceived. This leads to the conclusion that spatial rehearsal may amount to a successive allocation of attention to internal representations of spatial locations, a process possibly mediated by premotor mechanisms near the frontal eye fields. This region, together with parietal cortex, may also play a role in maintaining the representations of the spatial locations as well, a conclusion that is consistent with lesion studies and electrophysiological studies of monkeys in spatial working memory tasks. So, we can see that although storage and rehearsal are common features of spatial and verbal working memory, they appear to be implemented in the brain in different ways.

Of course, visual information that is stored need not be spatial in nature. Features such as the shape of an object or its color are not spatial, even though they are visual. As described above, the brain honors this distinction in simple visual processing, and indeed, neuroimaging research suggests that spatial memory and memory for other visual information are processed differently in the brain, as well. One experiment that demonstrates this used pictures of three faces presented sequentially in three different spatial locations. After a retention interval, a probe picture was presented in one of the locations. When subjects were tested on their working memory for objects, they had to decide whether the probe face was the same as any of the previous three; when they were tested on spatial working memory, they had to decide whether the probe was in the same location as one of the original faces. The elegance of this design is that it involves the very same stimuli, and only the nature of the memory task changes. The results show that this change in task produces an important difference in brain activation: The object task activated regions of dorsolateral prefrontal cortex, whereas the spatial task activated a region posterior to this, in premotor cortex. Beyond this, a meta-analysis of several spatial and object working memory tasks suggests that there is also a dorsal-ventral difference in activation in posterior cortex. Spatial working memory tasks activate more dorsal structures in posterior cortex, while object working memory tasks activate more ventral structures.

Executive Processes. In addition to storage components, the model of working memory proposed by Baddeley includes a component due to executive processes. Although there is not yet a clear taxonomy of

executive processes in hand, descriptions of them typically include: (a) focusing attention on relevant information and inhibiting attention from irrelevant information; (b) scheduling processes in tasks that require multiple processes; (c) planning and prioritizing a sequence of steps to meet some goal; (d) updating and checking the contents of working memory; and (e) coding internal representations for time or place of occurrence. All of these processes involve manipulation of information that is temporarily stored in working memory. Research on executive processes using neuroimaging techniques has revealed a heavy contribution of frontal mechanisms regardless of the executive process in question.

As an example, recall the verbal item-recognition task. In that task, subjects are presented a set of letters that they have to retain for several seconds, after which they have to decide whether a probe letter matches one of the letters in memory. Several recent studies have introduced an inhibitory component in this task in the following way. Trials were included in which the distractor probes (probes that did not match an item in the current memory set) were letters that did match a letter in the memory set from the previous trial. Thus, these probes were relatively familiar because they had recently been memorized. This design creates a situation in which participants have a sense of familiarity about the probe item, but they must remember that it doesn't match the memory set on the current trial. On such trials, subjects take longer to give a "no match" response. Both PET and fMRI studies show that there is a site in left lateral prefrontal cortex that is activated on these trials, and the activation occurs most prominently at the time the probe is presented. Furthermore, older subjects, who show a greater interference effect on these trials, also show less activation at this left lateral site. And patients with damage to this area show a dramatically increased interference effect compared to patients with damage elsewhere in frontal cortex. Taken together, this evidence suggests that the left lateral site is involved in resolving the conflict between familiarity and source memory that arises on these trials.

Another example of a task in which executive processes interact with storage processes is the 2-back task described above. Recall that in this task, single letters are presented in succession, and subjects must judge whether each letter matches the one two earlier in the sequence. To succeed at this task, one has to not only store the recent stream of letters, but one also has to update this stored set as new letters are presented, dropping older letters and adding newer ones. This task is similar to the item-interference task in that it

includes an inhibitory component, as described above. In addition to this executive process, the letters that are stored in memory also have to be tagged by their order of appearance so that the subject can keep in mind which one is 2-back, which 1-back, which 3-back, and so on. Thus, the 2-back task must recruit an executive process responsible for temporally tagging information, a sort of short-term episodic memory requirement. Indeed, the 2-back task shows evidence of activations in dorsolateral prefrontal cortex in addition to other sites that may well be responsible for temporal tagging. The dorsolateral prefrontal activation that arises in this task seems to be a common broad site of activation in many tasks that require manipulating the information stored in working memory, and so this leads to the general conclusion that prefrontal mechanisms may be responsible for a wide array of executive processes.

Summary of Working Memory. Overall the neuroimaging research concerned with working memory has reliably revealed a set of structures that may be important for storage, rehearsal, and executive processes. Posterior parietal mechanisms have been implicated in the storage of verbal material, and prefrontal ones concerned with language processing have been implicated in the rehearsal of stored verbal material. For spatial material, the sites of storage and rehearsal are different, but nonetheless, one can conclude that there are storage and rehearsal processes for nonverbal material as well, but that these may be implemented via non-linguistic mechanisms. Finally, various sites in prefrontal cortex, most prominently dorsolateral prefrontal areas, have been documented in the mediation of executive processes. Thus, the psychological architecture proposed by Baddeley in his model of working memory seems amply supported by a brain architecture that may honor the same distinctions among processes.

Episodic Memory

As described above, episodic memory can be defined as memory for information that is associated with a time and place of occurrence. Take as an example a semantic fact: you may know that the turn of the century French impressionist painter Claude Monet lived and worked for many years in his provincial home at Giverny. This fact is in the domain of semantic memory. However, your memory of learning this fact in your art history course would be an episodic memory. Episodic memory is often studied in a controlled laboratory setting using recognition or recall tasks, described in the introduction to this chapter. These tasks require memory for a source code (e.g., time or place of occurrence) that is the essence of episodic memory. In the context of

neuroimaging, the encoding and/or retrieval phases of these tasks are scanned using PET or fMRI and then compared to a control task with a diminished or absent demand on memory.

These studies have identified a set of regions underlying episodic memory. These include medial temporal structures, such as hippocampus and parahippocampal areas, prefrontal cortex, anterior cingulate cortex, cerebellum, and parietal and superior temporal association cortices (shown in Figure 2). Important hemispheric, regional, and functional differences exist, however, between the encoding and retrieval phases of episodic memory. In addition to exploring these differences, neuroimaging studies have also begun to examine cases in which this system performs inadequately.

Episodic Encoding. As discussed above, memory entails three important general stages: encoding, storage, and retrieval. At the encoding stage, processes must be involved that create an internal code for a piece of information, and then attach a context (a place or time) to the new memory.

Several neuroimaging studies have scanned participants while they perform some task to encode a set of items. For example, participants might be asked to make a judgment about whether a word represents an animal or vegetable, an encoding task that requires access to the semantics of the word. Alternatively, a subject might simply be asked to memorize a set of items and be tested on them later. Subsequent testing of the items confirms whether subjects have effectively encoded the items. These studies show that encoding involves left prefrontal cortex, hippocampus, parahippocampal cortex, anterior cingulate, and some superior temporal cortex. Further experimentation, including converging evidence from neuropsychology and other experimental paradigms, has begun to examine the role of each of these regions and their relationships to one another.

The hippocampus and surrounding areas have long been associated with memory. Evidence from both animal studies and studies of brain-damaged patients has shown that damage to the hippocampus can result in amnesia, one form of which is caused by damage to medial temporal structures such as the hippocampus and parahippocampal gyrus. Though amnesics are typically able to retrieve memories from their distant past, they show a profound deficit in the ability to form new memories, a phenomenon known as anterograde amnesia. For this reason, the hippocampus is thought to be involved with the encoding and consolidation of long-term memories.

In line with this, many neuroimaging studies using the encoding paradigms described above have

shown hippocampal activity. Recent neuroimaging evidence has shown, however, a selective response of the hippocampus to novelty. In one experiment, participants were shown pictures of indoor and outdoor scenes while in the MRI scanner. They were required to judge whether each scene was an indoor scene or an outdoor scene and remember the pictures for a later test. In some scans, the same two pictures were repeated many times so that participants became very familiar with them. During other scans, the scenes were entirely novel and unfamiliar. Comparing the unfamiliar scans to the familiar scans showed activity in parahippocampal gyrus bilaterally. Given this fact, it would seem that the medial temporal lobe is particularly responsive to novel stimuli—a finding consistent with the intuition that most episodic memory encoding occurs on the first presentation of new material.

The function of left prefrontal cortex appears to involve processing the context (or source) in which new information is learned. An event-related fMRI experiment has studied the different functions of left prefrontal and hippocampal mechanisms in episodic memory. Event-related fMRI allows the examination of areas of the brain that are active in response to different events occurring within the context of a single cognitive task. In this experiment, participants were required to learn word pairs in which the first word served as semantic context for a second word, for example “athlete-boxer”. Participants were presented with several of these word pairs during each scan. Sometimes the context for a word would change, as in “dog-boxer”. Other times the word would change as in “dog-labrador”. Both word and context could also be new, or both could be old. This design permitted independent manipulation of the novelty and the context of the item to be learned during encoding. The hippocampus was active when either the context word or related word was new, and it was most active when both were new. This corroborates the idea that the hippocampus is involved in processing novel items. The left prefrontal cortex was most active when an old context was attached to a new word or a new context to an old word. This finding suggests that the prefrontal cortex is involved in representing the context of the item to be remembered, a function that is critical for episodic memory.

We can test whether the effectiveness of encoding is related to the brain activations that reflect encoding by varying what is called the depth of processing participants apply to material. It is well known that evaluating the semantic content of material (‘deep encoding’) leads to more elaborate processing and a longer lasting memory trace than evaluating the physical features of material (‘shallow encoding’). One experiment that takes advantage of this effect required

subjects to judge whether a word was abstract or concrete (deep encoding) or whether it was printed in upper or lower case characters (shallow encoding). Deeply encoded words were remembered better than words encoded shallowly, replicating previous behavioral results. When the two conditions were compared, it was found that there was greater activity in hippocampus and left prefrontal cortex for deep encoding, suggesting that both areas are more vigorously involved with deep than shallow encoding.

This result by itself does not indicate that more activity in prefrontal cortex and hippocampus produces better behavioral performance; it only indicates that depth of encoding and activation are correlated. To address the performance question, several studies have directly examined the relationship between performance on retrieving an individual item in memory and brain activation while encoding that item. After being scanned, the participants had to recognize the encoded items, and they were grouped by whether they were correctly or incorrectly retrieved, an indication of good or poor encoding. This comparison revealed activity bilaterally in hippocampus and in left prefrontal cortex. Hence, it would seem important that for effective encoding, not only must the information be consolidated effectively by the hippocampus; it is also important that the prefrontal cortex assist in processing the context.

To summarize, encoding recruits a set of regions that include left prefrontal cortex, hippocampus, parahippocampal gyrus, parietal cortex, and anterior cingulate (as shown in Figure 2). These regions appear to be involved in transforming information into a mental code in the brain which can later be retrieved. Two processes entailed by this task are the consolidation of a novel item by the hippocampus and processing its context by the left prefrontal cortex. The extent to which the information being encoded can be effectively recovered at a later time is strongly dependent on the depth of encoding which seems to have an effect on the activity of the hippocampus and left prefrontal cortices.

Episodic Retrieval. Retrieval of episodic memory is mediated by regions that are generally functionally and anatomically distinct from those used in encoding. Most neuroimaging studies of retrieval use a similar task design as used in studies of encoding, in which participants must study a set of items and are subsequently tested for their memory of the items. The difference is that participants are scanned while they retrieve (recall or recognize) rather than while they encode the material. In recognition tasks, an item is shown, and it is the task of the participant to indicate whether that item was presented

during the study phase. Hence, it is necessary only to access the source and not the item as well. In recall tests, it is necessary to generate the item as well. Neuroimaging studies of both recall and recognition typically show activity in right prefrontal cortex, hippocampus, medial as well as inferior parietal cortex, anterior cingulate and cerebellum. There are some important variations in this pattern, however, that are discussed below.

The hippocampus is typically considered to be involved in the consolidation of long term memories, as discussed above. Although this function implies that the hippocampus should not be involved in retrieval, some studies *have* found it activated during retrieval tasks. To test whether the effort required for retrieval might influence activation of the hippocampus, one study varied the amount of effort required to search memory. In a "high-recall" condition, words were deeply encoded and, hence, less effortfully retrieved. When the recall phase was scanned, this manipulation revealed activity in the hippocampus bilaterally, supporting the view that the hippocampus is involved in effortless, conscious recall. In a "low-recall" condition, words were encoded more superficially, and hence, required more effortful retrieval. Scanning during this more effortful recall phase showed bilateral prefrontal but not hippocampal activation. Finding that the prefrontal cortex is involved in effortful retrieval is consistent with the view that one function of the prefrontal cortex is to implement retrieval strategies. The hippocampus, by contrast, may be involved in relatively more automatic retrieval.

Certain neuroimaging studies of episodic retrieval have found not only increased activity in right prefrontal cortex but decreased activity in other areas such as left prefrontal cortex. Based on this effect, some have suggested that episodic retrieval is not just an active process of search and retrieval, but involves the active inhibition of certain regions of the brain by other areas of the brain. By this model, right prefrontal cortex could be actively inhibiting left frontal regions as well as inferior temporal regions, areas that sometimes show deactivations in retrieval tasks. In the case of the temporal regions, for example, this might indicate the suppression of language processes during episodic retrieval. This effect has been termed "ensemble inhibition", and suggests that episodic retrieval may be carried out, in part, by inhibitory processes.

Retrieval processing involves an interplay between the right prefrontal cortex and hippocampus in the implementation of search strategies and conscious, effortless retrieval respectively. The involvement of other areas of the brain such as the precuneus, parietal cortex, anterior cingulate, and cerebellum have yet to be fully elucidated, so much further research is required on

this problem.

Synthesis: The HERA model and its extension. There appear to be stable differences in the activations accompanying encoding versus retrieval. The most striking pattern is in the activity of the prefrontal cortex. Most studies of encoding have shown activity in left prefrontal cortex, at a more anterior site. Whereas, most studies of retrieval have shown activity in right prefrontal cortex, also at a more anterior site. This hemispheric difference in prefrontal activity in episodic memory is typically referred to as the Hemispheric Encoding/Retrieval Asymmetry model, or HERA.

Other areas of the brain have also been included recently in the HERA model. For example, the left cerebellum seems more active during retrieval than during encoding. The cerebellum's anatomical connections are predominantly with the contralateral prefrontal cortex (via the thalamus), so the coupling of right prefrontal and left cerebellar activations is not surprising. What function the cerebellum might be serving in the context of episodic retrieval is unclear. The cerebellum has long been associated with motor coordination and visuomotor skill learning. It is possible that the cerebellum is serving one of these general roles in effortful retrieval, but its exact role remains to be elucidated.

The association cortices have also gained some attention in regard to the HERA model. The left temporal cortex has been found to be activated in some studies of encoding while activation in right or bilateral parietal cortex has been documented during retrieval. These findings, though not entirely uncontroversial, seem to follow the HERA pattern, with encoding being a left hemisphere function, in this case in the temporal lobe, and retrieval being a right hemisphere function, in parietal cortex. There is a great deal of speculation as to what these areas are doing exactly. Some accounts claim that they are involved in some way in the execution of special encoding or retrieval strategies. In the case of the temporal cortex, this might be attaching some kind of mnemonic code to items to help ease of retrieval later on. Others suggest that parietal cortex is involved in perceptual aspects of retrieval, such as mental imagery. Further study is necessary to fully understand the functions subserved by these regions, as well as the way that they interact with the other areas of the brain that are active during episodic encoding and retrieval.

It must be noted that there are important exceptions to the HERA model's general description of the patterns of brain activity during tasks of episodic memory. The model does not do well in predicting patterns of activation in the hippocampus.

Hippocampal activation has been found unilaterally on the right and left, and bilaterally in tasks of both encoding and retrieval. The pattern of activity in the hippocampus is best described as being dependent on the type of material being encoded or retrieved, not on encoding and retrieval by themselves. This is shown by systematic patterns of activation depending on whether verbal or nonverbal stimuli are used in an experiment. Most experiments using verbal information have shown predominantly left hippocampal activity. In contrast, the right hippocampus or both hippocampi may be more active in encoding visual information. For example, a study in which people retrieved information about a spatial route through a town activated bilateral hippocampus. It should be noted as well that the material specificity of activations extends to prefrontal cortex. One area of prefrontal cortex often observed in studies of episodic memory does not follow HERA, but rather depends on whether the stimulus material is verbal or visuospatial, the former producing activation on the left and the latter on the right. So, even within prefrontal cortex, one region obeys the description given by the HERA model and another does not.

Overall, it does appear that many patterns of activity demonstrated in tasks of episodic memory follow an asymmetric hemispheric pattern in regard to encoding and retrieval. In prefrontal cortex, and in temporal and parietal association areas, activity in the left hemisphere is associated with encoding processing and activity in the right hemisphere is associated with retrieval processing. The cerebellum also shows a hemispheric asymmetry, but this is the reverse pattern, with left cerebellum engaged during retrieval. There are exceptions to this pattern, and these are seen in the hippocampus, posterior regions, and some anterior regions of prefrontal cortex as well. The patterns of activity in these regions are dependent on the modality of the information being processed—verbal information lateralized to the left hemisphere and visuo-spatial lateralized to the right—rather than encoding and retrieval processes.

False memories. Memories of our personal experiences are extremely vulnerable because memory is often not *reconstructive* but *constructive*. When retrieving an episodic memory, we try to reproduce the event as closely as possible, constructing the most plausible approximation. Consequently, we often incorporate aspects of the event that are close to the original but not exactly it, and we can even insert information that never occurred at all. This vulnerability can even go so far as to produce elaborate situations that never actually happened, though the person might swear that they did.

Neuroimaging studies have begun to examine

differences in brain activation comparing retrieval of a true past event from false memory for an event that did not occur. Most of these studies have used a task in which participants are shown lists of words to study. After a long retention period, the participants are asked to perform a recognition task, indicating which words on a second list were present on the first list. Some of the words on the second list that were not present on the first list, called foils, are semantically related to the words on the first list. For example, the words “pajama, bed, night” might have appeared on the first list, but the word “sleep” might appear at the time of the recognition test. Semantically related foils were often falsely recognized as having appeared on the originally studied list. Furthermore, participants often rated their confidence that the words had been on the original list as highly as they rated their confidence that actual words had appeared. Thus, it appears as if the participants had created false memories of semantically related foil words.

Neuroimaging studies have compared activations due to falsely recognized words to activations due to correctly recognized words. One difference that emerges is activation in frontal cortex during true recognition. This is consistent with other retrieval studies, as reviewed above. Another feature of activation is that words on the recognition test that had actually been presented sometimes caused activation in the primary sensory cortex of the modality in which they had appeared. For example, a word presented aurally, when tested at the time of recognition, might show activation in superior temporal cortex. By contrast, words that did not appear showed no such sensory cortex activation. Thus, there is apparently a neural signature that permits one to distinguish actually presented words from semantically related foils, even if the subject does not access this signature in her recognition judgments.

Semantic Memory

Episodic memory is distinguished by the fact that it requires not only the retrieval of an item from memory but also a source or context for that item. But many times, we retrieve a fact with no knowledge of its context, as when we can identify various types of bicycles, without knowing when and where we learned about the various types. Semantic memory can be defined as memory for facts about the world, naked of their source context. This kind of knowledge plays a critical role in all forms of cognition, from language to reasoning to problem-solving. Hence, semantic memory is an important topic for study. Most studies of semantic memory have focused on the retrieval of semantic information from memory because this is

most readily studied and because it is more difficult, given the normal course of learning, to study encoding or storage of semantic memory.

Verbal Semantic Memory. Many of the concepts that make up our semantic knowledge are coded in the form of language, probably because we are such intensely linguistic creatures. These concepts come from various categories, of course, such as living things and nonliving things, distinctions that we can readily make for many concepts. There is evidence from patients with focal brain injury that the brain seems to honor some of these categorical distinctions among concepts. For example, there are patients who appear to have lost their ability to identify living things, such an elephant or a flower, even though they are still capable of identifying nonliving things, such as tools. One interpretation of this result is that the brain’s organization of semantic memory is, in part, organized by broad categories. To test whether this is so in normal adults as well as brain-injured adults, one study used PET to examine what areas of the brain are active during the retrieval of three different semantic categories. Participants were given several scans in each of which they were asked to name photographs of either famous people, animals, or tools. As predicted, different brain activations resulted from naming each kind of stimulus. Naming famous people produced activity in the most anterior part of temporal cortex, called the temporal pole. Naming animals produced activity in a more posterior area of temporal cortex in inferior and middle temporal gyri. Naming tools showed activity in an even more posterior portion of the inferior temporal gyrus. In general, the more specific the item that had to be named, the more anterior the activation in temporal cortex. These findings are consistent with the notion of a visual processing stream that spreads from occipital cortex into temporal cortex, moving from general classification to more specific categorization in anterior temporal cortex.

A related PET study of object and face naming provides corroborating evidence for these findings and further distinguishes between activations involved in the identification of specific faces versus simply recognizing stimuli as faces. In one condition, participants were asked to make gender discrimination judgments of familiar and unfamiliar faces. Relative to a control condition, this task produced activations broadly in extrastriate occipital cortex. Only when participants identified faces of famous people, and so had to make a specific face identification, were the temporal poles activated. Also activated were other structures in temporal cortex (fusiform gyri, right lingual and parahippocampal gyri, and left middle temporal gyrus) as well as orbitofrontal cortex.

Object naming in this study shared some common areas of activation with face naming, including orbitofrontal cortex, left middle temporal gyrus and left fusiform gyrus. Converging evidence from animal and lesion studies may shed light on the roles of these regions. Neuropsychological data suggest that the left middle temporal gyrus may be necessary for naming, but not recognizing, objects and faces. Lesions of orbitofrontal cortex have been related to visual memory impairments in animals. Finally, the fusiform gyri appear to be involved in recall of both faces and objects, with face recognition activating the right gyrus and object recognition the left. Interestingly, the fusiform gyrus has also been implicated in the *perception* of faces and objects, so the regions responsible for semantic memory for this type of information may be similar to the region used to perceive it. This hypothesis is supported by intracortical electrode studies done on patients, in preparation for possible surgery to treat epilepsy. These recordings showed that face recognition elicited electrical activity in the fusiform gyrus, and that electrical stimulation in this same region resulted in an inability of the patients to name a face for the duration of stimulation.

These complementary results suggest that face perception and recognition share a common substrate, and that the boundary between perception and semantic memory may be indistinct for this type of material. Studies of object naming more generally show that semantic memory about concrete objects appears to be organized, at least to some degree, in cortical modules devoted to particular types of remembered material, and these become more specific moving from posterior to anterior brain regions.

Semantic memory for words must take on more than just a simple recognition and naming function. Indeed, when faced with an object it is often more useful to know what can be done with that object, than just what the name of the object is. This type of information, as well as information about concepts that are not concrete, are within the domain of semantic memory and have been directly studied.

To examine this sort of semantic memory, a PET experiment was designed that required participants to generate an associated verb for each word in a list of nouns. For example, shown a picture of an apple, a participant might respond, "eat". This experiment revealed a preferential role of lateral and inferior frontal cortex in the generation of verbs associated with visually presented objects. It has been suggested that verbs are at the core of semantic structure, and hence activation in frontal cortical areas might be an indication of which areas are critical in mediating the

generation of semantic concepts. Further study of this verb-generation situation compared a task in which participants had to name a verb for each noun presented to two control conditions—reading words and passively viewing words. Multiple subtraction conditions were used to identify areas related to the motor execution of speech (motor cortex), word reading (left insula), and verb generation (left frontal cortex, anterior cingulate, and right cerebellum). This study also revealed changes in activation with practice on this task, as reviewed below. The constellation of regions that were activated in this study probably included a complex combination of areas involved in attention, inferential reasoning, willed action, episodic encoding, and working memory, but most prominently, there was significant activation in left prefrontal cortex and elsewhere that could be attributed to semantic retrieval.

Cognitive Skill Learning

Investigating practice-related changes in the verb-generation task provides a convenient segue into a discussion of skill acquisition—another vital aspect of memory. After 15 minutes of practice on the verb generation task, 90% of the verbs that participants generated were rote responses that had been consistently associated with the nouns. Participants no longer had to search through memory for a novel association; instead, they could quickly recall a response they gave previously. Analysis of the difference between the PET images early and late in the verb generation task showed that with practice, activity decreased in the anterior cingulate, left prefrontal cortex, bilateral inferior frontal gyrus, left temporal cortex, and right cerebellum—the very areas that were active when comparing verb generation to word reading. In fact, after practice the PET images were indistinguishable from those of word reading. Increases in activation with practice were observed in the precuneus and cuneus on the medial wall of the posterior cerebrum, and in right superior parietal cortex. These shifts in activation could be due to decreased demand on attention and effort, decreased searching of semantic memory, or some other factor.

Without further evidence, it is hard to distinguish among these. Certainly there is evidence that some of these areas are involved in other cognitive processes. For example, the left prefrontal cortex is activated in verbal working memory tasks and in the encoding of long-term memories, as we reviewed above. The anterior cingulate is also activated in some overpracticed motor tasks, particularly when they might require attending, making inferences about a pattern, or anticipating future stimuli or feedback. One region that may have a clearer role in the practice effect seen in the

verb-generation task is the insula, an area located anatomically near the region responsible for speech output, and an area that showed increased activation in the verb generation task with practice. This activation may be an indication of increasing automaticity in producing verb-associations given nouns as stimuli, a kind of stimulus-response connection that developed even over the course of relatively little practice.

Of course, one might ask whether skill in the verb generation task is a good example of cognitive skill learning in general. The shifts in activation in this task seem to result not from an improved ability to generate *novel* verbs, but rather from the ability to call up from memory the same verb the subject gave on the last trial, a kind of automatic stimulus-response mapping. It is not yet understood how true cognitive ‘skills’, such as the ability to make inferences and manipulate abstract concepts—are learned, except that their appearance in children seems to parallel development of the frontal lobes. However, a great deal of what we normally consider to be cognitive skills, such as expertise in chess, can be explained as the formation and retrieval of ever larger and more complex sets of associations in semantic memory.

A final example of cognitive skill learning comes from a PET study of categorization. Experimental studies have shown that people learn to categorize objects in several ways: through application of rules, learning of specific exemplars of a category, and implicit learning of an average or ‘prototype’ of the category. Patients with medial temporal damage, who have virtually no remaining episodic memory, fail on rule and exemplar-based categorization but learn prototype-based categorization as readily as do normal participants. In the study, people classified pictures of contrived animals based on previous practice with similar (but not identical) animals. One practice group learned to categorize animals by a rule, and the other group learned the categories by trial and error. The rule group categorized the new animals presented during scanning by applying the rule. The trial-and-error group categorized animals during PET scanning based on their similarity to the animals they saw during training, an exemplar-based strategy. Only rule-based categorization activated bilateral parietal cortex, right prefrontal cortex, and bilateral supplementary cortex, possibly reflecting greater working memory demands, attention shifting, and retrieval and application of the rule. Exemplar-based categorization activated left extrastriate cortex and left cerebellum. The extrastriate activation may reflect greater use of a perceptually based memory trace in the exemplar-based strategy, consistent with the involvement of extrastriate visual cortex in studies of implicit

memory. This study suggests that different learning regimens may have a profoundly different effect on the brain circuitry recruited to the task, at least for a task requiring categorization processes.

Learning Procedural Skills

Procedural knowledge, as described above, consists of knowledge of how to do something. It includes all the behaviors shown as examples of procedural knowledge in Figure 1, all of which share in common that they do not require explicit retrieval of information; rather, they require the person to tap memory in the service of some other task, such as riding a bike taps memory to coordinate the muscles in various ways so that balance can be maintained. This is often called “implicit” memory. Viewed this way, it is clear that a vast number of motor skills are mediated by procedural memory. Of course, procedural memory must develop over the course of practice, and the changes that occur with practice are often highly specific, improving performance on precisely those tasks we practice. Although this may seem to limit our behavioral repertoire, in fact, once we have learned a sequence of motor movements, we can quickly learn to adapt these movements to similar situations.

Skill learning occurs when a new movement or sequence of movements is acquired, and performance becomes both faster and more accurate with training. Sometimes, this learning might involve the acquisition of new sensory-motor mappings. Studies of motor skill learning have focused on either the acquisition of some new sequence of motor movements, such as a sequence of finger taps, or on the acquisition of some sensory-motor mapping, such as guiding a visual cursor with joystick movements.

A note: it is often difficult to separate the brain areas involved in learning a skill from those involved in other aspects of processing that change along with skill learning. As people learn a skill, for example, they devote less attention to the task, and so neural circuitry responsible for focusing attention is less involved. At the same time, the incidence of errors decreases, so the brain activity related to error detection and correction will decrease. The brain regions responsible for mediating task performance may also change as skills become automatic. All these changes obscure the interpretation of neuroimaging studies of the learning process by making it difficult to determine which activations are due to skill-learning per se and which are due to other processes.

Motor skill learning. Execution of motor tasks such as tapping your fingers in a particular sequence or maintaining contact between a target moving in a circular pattern and a hand-held marker activate large

regions of cerebral cortex and subcortical structures, including sensory motor cortex (primarily the primary motor cortex), supplementary motor area (SMA), premotor area (PMA), putamen, cerebellum, and sensorimotor thalamus (see Figure 2). Traditionally, and consistent with data on the anatomical layout of the motor system, neuroimaging studies have found activations in these areas on the side contralateral to hand movement (with ipsilateral activation of the cerebellum because of its crossed connections to cortex). However, recent evidence indicates that complex movement of even one hand can activate motor areas bilaterally. For example, in one experiment, participants rotated two metal balls at a constant rate in either their right or left hand. These complex movements activated the regions mentioned above, including significant bilateral activations in the postcentral gyrus, traditionally considered primary somatosensory cortex, and intraparietal sulcus. Notably missing from this list of activations is the basal ganglia, which appear to be preferentially activated during performance of learned sequences of movements.

Areas involved in the learning of motor skills are largely the same areas as those used during task performance. However, some regions become active only during initial learning, or only after performance has become automatic and requires little effort. These changes are specific to the type of task—they vary depending on whether automatic performance involves increased or decreased use of sensory cues and whether learning involves learning a new movement, a sequence of movements, or a sensory-motor association.

Sequence learning. Among the first motor learning tasks studied is the sequential tapping task, in which participants must tap the fingers of their dominant hand (all studies reviewed here used right-handed subjects) in a pre-specified sequence. An early study scanned participants doing sequential finger tapping at three stages in the learning process. The three levels corresponded to an initial learning phase when a skill is first being learned, the phase when a skill becomes automatic after significant practice, and skilled performance after performance level has reached its asymptote. The ipsilateral (right) cerebellum was activated in all three conditions, and the activation per movement in the cerebellum decreased as training progressed. The striatum was also activated during advanced practice, suggesting a role for the basal ganglia in the development of automaticity.

Subsequent studies of sequential finger tapping have examined the role of the cerebellum and

other structures, including changes in primary motor cortex, in more depth. Unpracticed performance activated a network of areas often associated with the planning and execution of movements: contralateral primary motor cortex and putamen, bilateral PMA and SMA (with more activity on the contralateral side) and cerebellum. With practice, activity decreased in the lateral portion and deep nuclei of the cerebellum, supporting the view that the cerebellum is important in sequence learning and may be less important in execution of highly learned sequences.

Subsequent studies examined activations during a sequential finger-tapping task in which participants had to learn the correct sequence by trial and error. The first study compared activations between new sequences, learned sequences, and a resting control. Similar to the earlier studies, performance of learned sequences with some degree of automaticity activated contralateral (left) primary motor cortex, PMA, SMA, putamen, and bilateral cerebellar hemispheres, vermis, deep cerebellar nuclei, anterior cingulate, parietal cortex, and ventrolateral thalamus. Of course, as sequence performance was compared with a resting condition, this network includes areas responsible for processes irrelevant to sequence learning. When compared to rest, performance of new sequences showed, in addition to these areas, increases in prefrontal cortex and more extensive activation of cerebellum. When compared to the practiced sequence directly, learning of a new sequence produced activations in bilateral PMA, cerebellum, anterior cingulate, prefrontal cortex, and medial thalamus. It seems likely that the requirement to infer the correct sequence based on error feedback was responsible for the activation of the anatomically interconnected prefrontal-anterior cingulate-medial thalamus network. However, as we will see later, it is possible that the cerebellum also contributes to error detection and correction.

In another revealing manipulation, participants were asked to pay attention to their finger movements while performing a highly learned sequence. Attention resulted in the reactivation of the anterior cingulate and prefrontal cortex. Comparing learning of a new sequence with a control condition that required a similar level of attention and similar decision and motor processes, they found activation of the caudate nucleus and the cerebellum. This result indicates that these two structures may be important in learning a new sequence, as opposed to other task-related processes. Together, these studies suggest that the basal ganglia and cerebellum, and possibly the PMA, are involved in skill learning, whereas anterior cingulate and prefrontal areas are involved in attention and higher-level control processes.

A more controlled version of the tapping task is the Repeated Sequence Task. In this task, participants see a cue appear above one of four squares, and they must touch that square as quickly as possible. As a particular sequence appears more frequently, participants become faster in pressing the appropriate squares. The faster responses for the learned sequence indicates that implicit learning of the sequence has occurred, even though participants have no explicit, declarative memory for the sequence.

Doyon and coworkers, using this paradigm, compared PET activation among several conditions, including different amounts of learning, and included a condition in which subjects were given explicit knowledge of the sequence prior to scanning. Performance on highly learned versus random sequences resulted in increased activation in the right (ipsilateral) ventral striatum, right cerebellum, anterior cingulate bilaterally, right medial parietal cortex, and right extrastriate cortex. Decreases were found in the ventrolateral frontal, frontopolar, and lateral parietal cortices, all on the right side. As with previous studies, basal ganglia activity increased when performance was highly learned. These changes are consistent with recent animal models suggesting a role for the basal ganglia in performance of movement sequences.

When compared with newly learned sequences, highly learned sequences showed increased activity in the cerebellum, suggesting a role for the cerebellum in sequence performance or in the development of automaticity. This finding contrasts with previous sequence learning studies, which found that cerebellar activity decreases as performance becomes automatic, so further research is necessary to investigate the role of cerebellum. It is possible that the cerebellum has multiple roles and plays a part both in initial learning and in later retrieval of sequences. An alternative explanation for cerebellar activity in the learned – unlearned comparisons in these studies is that the cerebellum is required for speeding up movements while maintaining a criterion level of accuracy. In the early stages of training, it may be difficult to keep movements in time, resulting in cerebellar activation that decreases as it becomes easier to perform the task at the requisite speed. This hypothesis highlights the fact that neuroimaging results may be interpreted in multiple ways.

Newly and highly learned sequences in the Repeated Sequence Test were also examined before and after participants were given explicit knowledge of the sequence. Explicit knowledge of highly learned sequences relative to implicit performance decreased signal in the right (ipsilateral) cerebellum and

increased activation in the right ventrolateral frontal cortex. Explicit versus implicit knowledge of newly learned sequences resulted in increased activation of the right cerebellum and left ventrolateral frontal cortex.

The sequence-learning studies reviewed here implicate the cerebellum and basal ganglia in initial learning and automatization of new skills. Three studies found significant activity in the basal ganglia with practiced, but not novel, sequences. Two other studies found basal ganglia activity in newly learned sequences, one relative to a resting control and the other relative to a free-selection tapping task. The cerebellum appears to be involved in early learning of the sequence, but it is also active during skilled performance relative to rest. Its activity may increase as participants gain skill if that skill involves making speeded responses to visual cues.

Notably, none of these PET studies showed changes in primary motor cortex as a function of practice. However, some researchers have shown that skill learning produces nonmonotonic changes in the strength and spread of activation within primary motor cortex. These researchers scanned participants learning one of two similar finger tapping sequences using fMRI. Initially, a habituation effect to sequence performance was found: activity in primary motor cortex was lower when it was performed later in the scanning block. After 30 minutes of practice, activity in primary motor cortex was higher when it was performed later in the scanning block, but only for practiced sequences—possibly reflecting fast learning processes that set up later consolidation of a new motor sequence. After four weeks of daily practice, more areas in primary motor cortex were recruited during performance of the learned sequence, showing that practice resulted in a true expansion of the cortical area recruited in primary motor cortex.

Learning sensory-motor associations. What are strikingly missing from analyses of sequence learning, but apparent in other motor learning tasks, are changes in activation of premotor and supplementary motor cortices. Studies of sequential finger-tapping primarily require the learning of associations between movements that form a sequence. This kind of learning may be fundamentally different from learning that requires improvement in coordination or learning an altogether new motor movement. In addition, the finger tapping task requires a series of internally generated movements rather than movements elicited by sensory cues. We have already seen that learning in the Repeated Sequence Test, which involves visuo-motor associative learning, may produce a different pattern of cerebellar activity than learning of internally generated movement sequences. Perhaps examination of non-sequence motor learning, including studies of rotor pursuit, trajectory

movements, joystick movements, and maze tracing may help resolve discrepancies.

Rotor pursuit involves maintaining contact between a hand-held stylus and a target moving in a circular pattern. Several studies have compared rotor pursuit with visual tracking of the stylus, identifying changes due to skill learning of the appropriate hand movement. An initial study showed increases with practice in primary motor cortex, SMA, and the pulvinar nucleus. In a later study, PET scans over two days of learning revealed a similar pattern of activation on day 1, this time including practice-related changes in ipsilateral cerebellum, cingulate, and inferior parietal cortex. On day 2, after an extensive practice period, the rotor pursuit – visual tracking subtraction revealed changes in the putamen and parietal cortex bilaterally, and the left (contralateral) PMA. Improvement on the task was correlated with increased activity in premotor, prefrontal, and cingulate areas, and decreased activity in visual processing areas.

An opposite pattern of changes in the PMA and SMA were observed in a series of studies of maze tracing. In the maze tracing task, participants practiced tracing cutout maze patterns with their eyes closed. Tracing a novel maze with the right hand in a clockwise pattern (relative to a control) resulted in increases in right PMA and left cerebellum. Practice diminished both these loci of activity: PET scanning after 10 minutes of practice produced increases in SMA and decreases in right PMA and left cerebellum. Contrary to expectations, training affected activity in the ipsilateral cerebrum and contralateral cerebellum. A follow-up study examined maze tracing with the left hand in a counter-clockwise pattern and, strikingly, produced the same results. A recent third study confirmed that only primary motor cortex and anterior cerebellum showed activation depending on which hand was used, suggesting that learning and performance in the maze-tracing task requires an abstract representation of movements and patterns not directly tied to motor activity.

Contradictory effects of practice in similar tasks, such as that found in PMA and SMA in the studies reviewed above, may reflect something of the underlying functions of premotor brain regions. It has been suggested that the SMA is active in the internal generation of responses, and PMA is preferentially active when responses are contingent upon sensory cues. That distinction can be applied to neuroimaging studies of human skill learning. In the rotor pursuit studies, learning a new motor skill resulted in increased activity in SMA. After the movement was automatic, PMA and basal ganglia were activated in adapting the movement to the motion of the stylus. In

the maze studies, initial performance relied heavily on somatosensory feedback from the cutout maze, and so PMA was heavily recruited. After the maze was well learned, a coordinated, internally generated movement could be used to successfully trace the maze without reliance on sensory feedback. This type of internally generated movement appears to be the domain of the SMA. Consistent with this view, neuropsychological evidence shows that patients with PMA damage are impaired in sensory-cued motor learning.

A study in which participants had to write the letter “R” found increases in right PMA and right parietal cortex, possibly indicating enhanced attention to sensory feedback. Again, the activation was unexpectedly ipsilateral to the hand used. When participants wrote the letter as quickly as possible, a network including left primary motor, PMA, SMA, and right putamen were activated. These experiments also compared writing novel ideograms with the right hand to a baseline in which participants watched the figures being drawn. Novel ideograms, as compared to baseline, activated left primary motor cortex and right cerebellum. Practiced ideograms minus baseline activated right PMA, left SMA, and right cerebellum. Once again, cerebellar activity appeared during the initial learning and automatization phases of new visuomotor patterns, but was not apparent when writing the letter “R”, a highly practiced ideogram.

These studies show increases in PMA when sensory feedback or external cues are critical for task performance. Right PMA increases appear to be modulated by task demands—e.g., asking participants to be accurate—and independent of the hand used. In the study of unilateral two-ball rotation mentioned above, positive correlations were found between unilateral PMA activity during movements of either hand and skill improvement for the ipsilateral hand. Skill improvement was measured during non-scanning intervals by comparing the maximum rotation speed of the balls just after the first scan and just before the last scan. The strongest correlation was between right PMA activity and skill improvement for the right hand. Correlations between left PMA and skill improvement for the left hand were also positive and significant.

The cerebellum appears to play a particular role in the learning of new visuomotor associations. In a classic study, participants made joystick movements to align a cursor with a visual target in one of three joystick-cursor mappings: normal mapping, reversed mapping in which joystick movements caused the cursor to move in the opposite direction, and random mapping with no relationship between joystick and cursor movement. The PET camera in this study was centered on the cerebellum, to allow maximum sensitivity to

changes in this structure. When the mapping between joystick movements and cursor movements was reversed, cerebellar activity was high during initial learning and decreased as performance improved. When the mapping between joystick movements and cursor movements was random, no learning occurred and cerebellar activity remained high. The authors concluded that the cerebellum contributes to visuomotor skill learning by participating in the detection and correction of errors. It should be noted, in closing, that the cerebellar contribution to skill learning may be primarily in sensory-motor association tasks. Patients with cerebellar atrophy can improve on some motor skill tasks, but they fail to coordinate and adapt movements to environmental contexts.

Learning perceptual skills. Research on the psychophysics of perceptual learning suggests that long-term learning of skills is not limited to motor areas. This research suggests three striking findings: that learning to detect a visual stimulus is specific to a retinal location, that it only occurs if the stimulus is behaviorally relevant, and that effects of learning remain robust after nearly three years without practice.

Although there has been relatively little neuroimaging research on perceptual learning, the research that has been conducted is illuminating. Perhaps the first study was an fMRI experiment of mirror reading. Participants viewed words and matched nonwords printed backwards and decided whether the stimulus was a real word. Improvement in mirror reading is still detectable after two months of practice, and changes in performance are evident after a year without practice. The researchers compared mirror-reading with normal reading and practiced mirror-words with unpracticed ones. Mirror reading compared to normal reading produced increases in blood flow in a number of areas, including medial and lateral occipital cortex, right superior parietal cortex, bilateral fusiform gyrus, pulvinar, and cerebellum, particularly on the right side. Decreases were found in nearby regions of some of the same areas, including medial occipital and right superior parietal cortex, as well as in precuneus and bilateral middle/superior temporal gyrus. The occipital, fusiform, and pulvinar areas form an anatomically interconnected network associated with visual processing, object recognition, and visual attention. The authors suggested that these activations were due to visual transformation of the letters in unpracticed mirror reading.

With practice, mirror reading activation increased in the precuneus, left superior parietal cortex and fusiform, and right cerebellum and superior

temporal gyrus. Decreases were found in a number of areas, including left lingual gyrus, bilateral occipital cortex, and right cerebellum, superior and inferior parietal, inferior temporal, and pulvinar. The deactivation of right superior parietal cortex and occipital cortex could reflect decreased involvement of attention, which is associated with right parietal activation in a number of studies, or it could result from a decreased need to rely on visuospatial transformations. Increases in the left fusiform gyrus, activated in at least one other letter recognition study and in studies of object recognition, could reflect a shift to direct letter-recognition processes. Overall, the results are consistent with a shift in strategy from sensory transformation to direct recognition of mirror words.

Implicit memory. All the studies of skill learning discussed above involved both explicit and implicit memory for motor activity. Although procedural in nature, in most of the tasks participants were allowed to develop conscious recognition of the sequences and movements to be learned. In one study, explicit awareness of a sequence was associated with changes in the cerebellum, ventrolateral frontal cortex, and medial frontal cortex. The remainder of the changes with skill learning, found prominently in parts of the cerebellum, primary motor cortex, SMA, PMA, and basal ganglia, presumably reflect changes in procedural motor processes: the kind you can do, but cannot describe—and, if you are amnesiac, may not remember that you ever learned.

Implicit memory is not limited to motor and perceptual learning, however. Exposure to words, pictures, faces, and other stimuli influences later processing of this information, even though subjects may not ‘remember’ any of the trained items. This unconscious memory is independent of explicit recollection, meaning that the amount of explicit memory one has for a stimulus does not predict the amount of implicit memory. Also, implicit memory is not affected by depth of encoding as is explicit memory. The two forms of memory appear to be separate species that operate independently of one another. Neuroimaging results support the conclusion that explicit memory and implicit memory are mediated by separate circuits in the brain—explicit memory by hippocampus, prefrontal cortex, and related circuitry, and implicit memory by perceptual areas similar to those discussed in the previous section.

One of the most common ways to study implicit retrieval is the word-stem completion task. In the encoding phase of the task, participants are given a list of words and asked to make some judgment, semantic or otherwise, about the words. Subsequently, the participants are given a list of incomplete words—such

as the first three letters—and asked to complete the fragments with whatever word comes to mind. If the fragments match words that they viewed before, participants are more likely to complete the stem with the previously viewed word, whether or not they consciously remember it.

Daniel Schacter and coworkers predicted that when only implicit memory is involved in a task, stem completion will not activate the hippocampus, the structure critical to explicit episodic memory. They asked participants to count the number of ‘T’ junctions in a list of words, and compared activation during stem-completion of words from the list with novel words. Participants did not explicitly remember the words, but their performance showed priming effects—and their PET scans revealed no hippocampal activation, but showed decreases in extrastriate (visual) cortex. In another study, they compared stem completion when participants had encoded words deeply (when they were required to make semantic judgments) or superficially (when they counted ‘T’ junctions). Explicit memory and hippocampal activation during stem completion were greater for the deeply processed words. Other studies have replicated this basic finding with object naming and categorization tasks. These results taken together indicate a dissociation between explicit and implicit memory; explicit memory involves activation of hippocampal structures, while implicit memory involves deactivation of posterior neocortex.

Studies in other domains of semantic knowledge, such as object categorization and object naming, show similar priming-related reductions in activation. One explanation of the decrease in activations is that repeated presentations lead to more efficient perceptual processing and lower levels of activation. However, in an auditory word-stem completion task studied by Schacter and colleagues, auditory presentation of words and auditory stem completion produced the same rCBF decreases in bilateral extrastriate cortex, as well as decreases in right anterior medial prefrontal cortex, right angular gyrus, and precuneus. Thus, priming effects on extrastriate cortex appear to be modality-independent.

Some Concluding Remarks

There has been remarkable progress in the study of memory during the last half of the twentieth century. The development of neuroimaging techniques has contributed in no small part to this progress. These techniques have provided a source of evidence about the relationship between brain structure and psychological function that complements evidence from the study of human patients with brain injury,

behavioral evidence from normal human subjects, and evidence from animal models. Taken together, these sources of evidence have sketched the outlines of complex of memory systems. These systems in their interaction form a seamless whole capable of dealing with a variety of cognitive problems. Our memory apparatus has multiple components (working memory, long-term memory), multiple representations of information in different formats (e.g., verbal versus spatial), multiple retrieval schemes (explicit versus implicit), multiple circuitries, and multiple processes (encoding, retention, and retrieval). We are far from getting our arms around a complete description of this system, but continued use of the full array of investigative tools promises much new progress in the current millenium.

Figure Captions

1. A taxonomy of various forms of long-term memory

2. Brain diagrams highlighting the major structures discussed in the text. The upper figure shows a lateral view of a left hemisphere of the human brain, and the lower figure shows a view of the right hemisphere as seen from the midline of the brain. Major structures of relevance to memory are labeled.

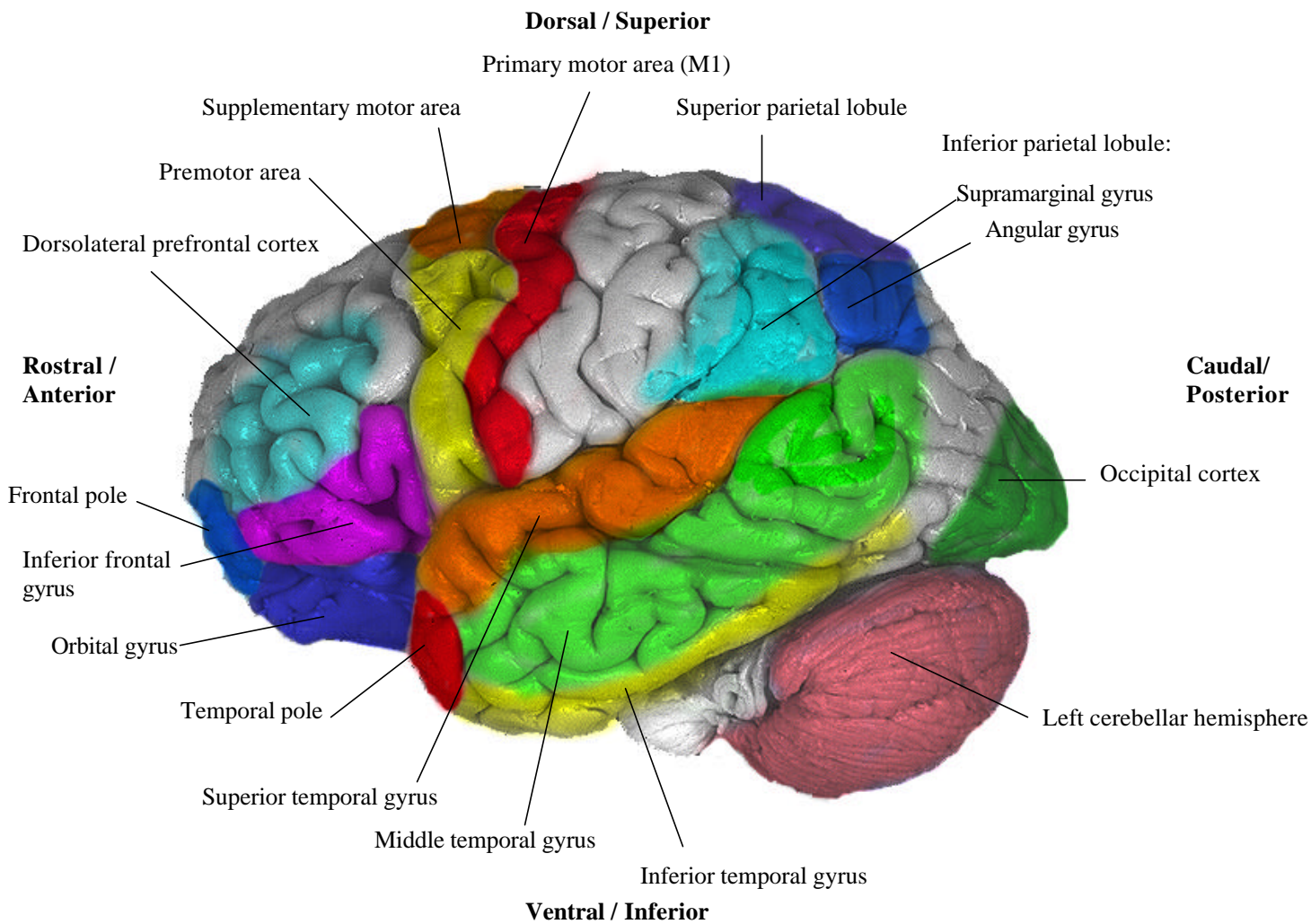


Figure 2, con't.

