

MEMORY

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The topic of this chapter is memory, broadly defined. Memory is a complex, multidimensional set of functions with numerous distinct forms that interact to provide the rich and diverse cognitive capacities that we possess. In this chapter, a broad overview is provided regarding the relationships between particular forms of memory and their associated neural substrates. In doing so, we use some of the currently accepted distinctions between forms of memory, such as the distinction between episodic memory and working memory. However, by doing so, we do not wish to imply that there is always a complete dissociation between the cognitive processes and neural systems involved across memory forms. Instead, we hope to convey the growing evidence that putatively different memory forms often share common processing elements and that many brain regions are important for multiple aspects of memory function. Such interactions are, quite frankly, just beginning to be understood. It should also become clear through the course of this chapter that damage to specific brain regions often leads to deficits in multiple memory domains rather than to isolated disturbances in specific forms of memory.

SUBDIVISIONS OF MEMORY

Researchers and theorists have long attempted to subdivide the construct of memory into multiple forms. Such attempts have included distinctions between episodic and semantic memory (186), declarative and procedural memory (43,203), working (short-term) memory and long-term memory (8), and implicit and explicit memory (169). In an attempt to summarize this literature, Schacter and Tulving suggested that there was evidence of the existence of at least five different major memory systems in humans, including the perceptual representation, working memory, semantic memory, episodic memory, and procedural memory systems (172). Several elements of these different memory forms are shown in Figure 18.1. One broad, first-level distinction particularly relevant to this chapter is the distinction between working memory and long-term memory (4).

Working memory has been defined as the ability to temporarily maintain and manipulate information over time (8). Long-term memory is used to refer to a diverse set of memory forms, some of which may be more related than others. In general, however, the term long-term memory is used to refer to memory forms that allow information to be available over extended periods of time (9).

Each of these broad divisions of memory has been hypothesized to include further important subdivisions and component processes. For example, within the domain of working memory, Baddeley's (8) influential theory distinguishes among three subcomponents, including short-term storage buffers for visual (visuospatial scratch pad) and verbal (phonologic loop) information, and a central executive component that guides the manipulation and transformation of information held within the storage buffers. To illustrate, holding a phone number in mind while dialing would require the phonologic loop, whereas remembering the locations of checkers on a board would entail using the visuospatial scratch pad.

Long-term memory has also been further subdivided, with distinctions commonly made between episodic memory (events), semantic memory (facts), and procedural memory (skills) (172). Episodic memory refers to the ability to learn and retrieve memories about personal experiences that are situated in a specific time and place (186). Semantic memory includes an individual's general knowledge about the world, including facts, the meanings of words and concepts, and the relationships among concepts and ideas. Semantic memory differs from episodic memory in that the information is not necessarily tied to any specific learning episode or context associated with that episode, as is the case for episodic memory (186). Procedural memory refers to the acquisition of new motor and cognitive skills (i.e., roller skating, reading), the contents of which may or may not be consciously available to the individual (151–153). For example, while learning to ride a bike, procedural memory would allow skills associated with riding to be acquired; semantic memory would support the knowledge of bike parts and rules of riding, and episodic memory would be required to remember the specific time

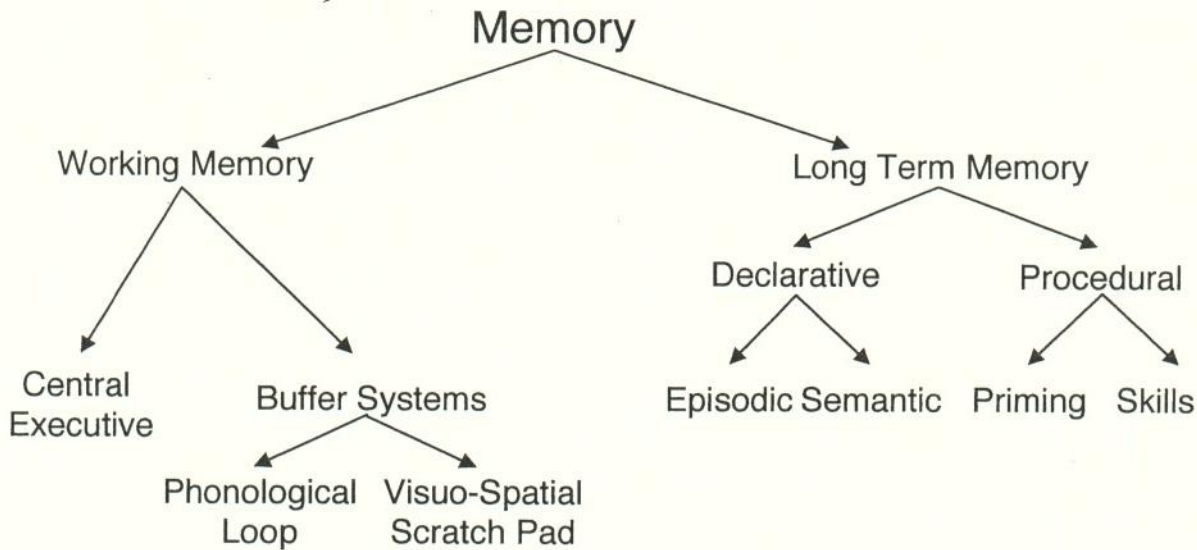


FIGURE 18.1. A schematic diagram represents a summary of different schemes for subdividing the construct of memory into dissociable subcomponents. (Developed in collaboration with Endel Tulving.)

and events associated with the first experience of trying to ride a bike.

The scheme for subdividing forms of memory outlined above is only one of several possible organizational systems suggested in the literature. In this review, the primary focus is on the functional neuroanatomy of working memory and two forms of long-term memory (semantic and episodic).

EPISODIC MEMORY

Episodic memory requires the coordination of a complex set of processes that involves the activity of multiple brain regions. Findings from both human neuropsychology research (i.e., lesion studies) and human functional neuroimaging research have identified multiple brain regions as being important for episodic memory. Historically, research has highlighted the contributions of the hippocampus and the surrounding medial temporal structures as being critical for the formation and retrieval of new episodic and semantic memories (44). One of the initial impetuses for the view that the hippocampal formation is critically involved in episodic memory is work with amnesic patients, such as H.M., who have had lesions to the hippocampus and/or surrounding medial temporal areas (173). After these lesions, such patients have profound deficits in the ability to learn and/or retrieve new episodic and semantic memories, despite relatively intact cognitive functioning in other domains (46,173,182). Nonhuman primate models of memory loss also demonstrate that lesions within the hippocampus and adjacent cortex (within the medial temporal lobes) result in an impaired ability to retrieve recently acquired information (118,203).

Several different theoretical models have been proposed to account for the role of the medial temporal cortex in memory formation. One theory is that the hippocampal formation is critical for the rapid binding of novel configurations of information and that this function is the basis of its role in episodic memory formation (44).

At the same time, a growing literature highlights the important contributions of prefrontal structures to episodic memory. Human neuropsychology research has shown that damage to the prefrontal cortex can also lead to episodic memory deficits, although episodic memory is typically not the only cognitive function impaired in these individuals. Instead, damage to the prefrontal cortex, depending on its location, can also lead to disturbances in language function and/or a variety of higher level cognitive processes, including planning, problem solving, inhibition, and working memory. Such results have led to the hypothesis that damage to prefrontal cortex impairs episodic memory by impairing strategic contributions to memory formation and retrieval (176), whereas hippocampal damage impairs the actual binding of information into new memories, a topic discussed below.

Research with individuals with Korsakoff syndrome has also brought to light the importance of diencephalic regions for memory function. Korsakoff syndrome is thought to result, at least in part, from a severe thiamine deficiency linked to the malnutrition that often occurs in chronic alcoholism. These individuals can display memory impairment that is as severe as those shown by individuals with bilateral medial temporal lesions (176,177). There are at least four major parts of the diencephalon, including the epithalamus, thalamus, hypothalamus, and subthalamus. Amnesia secondary to diencephalic damage (as is seen in Korsakoff syndrome)

is most frequently associated with damage to the dorsomedial nucleus of the thalamus, the mamillary bodies of the hypothalamus, and the mamillothalamic white matter tract (54). Functional neuroimaging studies of episodic memory also often reveal activation in these regions, but to date their precise contributions to episodic memory are unclear.

The advantage of neuropsychological research with lesion patients is that it is particularly helpful in identifying brain regions that may be necessary to carry out particular cognitive functions. However, the fact that damage to a number of different brain regions can lead to impairment of episodic memory highlights the fact that the construct of episodic memory itself contains multiple subcomponents. One clear subdivision to be found within episodic memory is the distinction between encoding and retrieval. Unfortunately, it is more difficult to identify brain regions involved in encoding versus retrieval in research with lesion patients because such lesions are often diffuse, affecting multiple brain regions, and because behavioral tasks used to measure memory impairment simultaneously often depend on both encoding and retrieval processes. It is in this domain that human functional neuroimaging research has been particularly helpful. Although functional neuroimaging research is less able to determine which brain regions are *necessary* for cognitive task performance, it can help to determine whether activity in specific brain areas is present only during encoding or during retrieval or both.

Episodic Memory Encoding

Prefrontal Cortex Contributions

Human episodic encoding has been explored in many studies using a variety of materials, including both verbal and nonverbal stimuli. Many of these studies have targeted correlates of brain activity associated with the active attempt to remember words or sentences (commonly referred to as intentional encoding). In such studies, participants are explicitly told that a memory test will follow and are directly instructed to try to memorize the materials. Results obtained from both functional magnetic resonance imaging (fMRI) and positron emission tomography studies consistently demonstrate that specific regions within the frontal cortex are active when subjects intentionally memorize or encode stimuli such as words, sentences, and faces (65,99,111,122). The issue of domain specificity (i.e., verbal vs. nonverbal materials) within frontal regions is raised in a later section.

Although episodic encoding paradigms in the laboratory often involve participants being explicitly aware of the need to memorize stimuli, most instances of episodic memory formation in everyday life occur incidentally, without any specific intention to remember. A long history of research in cognitive psychology (48,87,146) has shown that episodic memories can form as a by-product of particular forms of information processing, independent of the individual's intent

to memorize the information. For example, words that are elaborated on in terms of their meaning and how they relate to other words and concepts in memory are better remembered than words processed in a shallow fashion in which only surface characteristics are examined—the well-known levels of processing effect (48,64) [but see also Fisher and Craik (64) for important caveats on this principle]. William James, in 1890, noted this observation elegantly by suggesting that “the more other facts a fact is associated with in the mind, the better possession of it our memory retains.”

Functional neuroimaging research has demonstrated that prefrontal regions active during intentional memorization are also active during behavioral manipulations that incidentally encourage effective memory encoding through meaning-based elaboration, even when the participant is unaware of the need to encode. For example, when participants perform tasks that require meaning-based judgments of words (i.e., abstract/concrete, living/nonliving judgments), multiple regions within the left frontal cortex are activated. On subsequent surprise memory tests, the words on which these judgments were made are remembered, even though the participants made no direct attempt to memorize the words at the time of encoding (37,55,75,98,157,193). In contrast, when participants perform a task in which words are evaluated on surface level characteristics (i.e., are the letters uppercase or lowercase?), left frontal activity is reduced, and memory for the words is poor.

Further evidence of a link between left frontal activity and verbal encoding comes from neuroimaging studies that have examined neural activity at the time of encoding as a function of whether a particular item is subsequently remembered or forgotten. The idea for such investigations stemmed from early studies using electrical scalp recording techniques (60,130,158,192). These studies recorded event-related response potentials from subjects at the time of memorization and revealed differences for words that were later remembered compared with words that were later forgotten. Recent developments in fMRI methods [27,52,97,105,202; for a review, see Rosen (156)] have allowed similar phenomena to be examined with better spatial (anatomic) localization.

In many of the fMRI studies, participants performed tasks that encourage semantic processing of words without being told to expect a later memory test. A surprise recognition test was then administered, the results of which were used to identify the neural correlates during encoding of words that were remembered versus those that were forgotten. These studies have consistently demonstrated that regions of the frontal cortex are among those most strongly correlated with subsequent memory performance (2,10,22,23,37,102,125,194). For example, Figure 18.2 shows representative results from Wagner et al. (191), in which activity in the left prefrontal cortex along the ventral portion of the inferior frontal gyrus at the time of encoding was greater for words that were subsequently remembered than for those that were forgotten. Such findings provide compelling examples of a direct link

Sorting Based on Subsequent Memory Performance

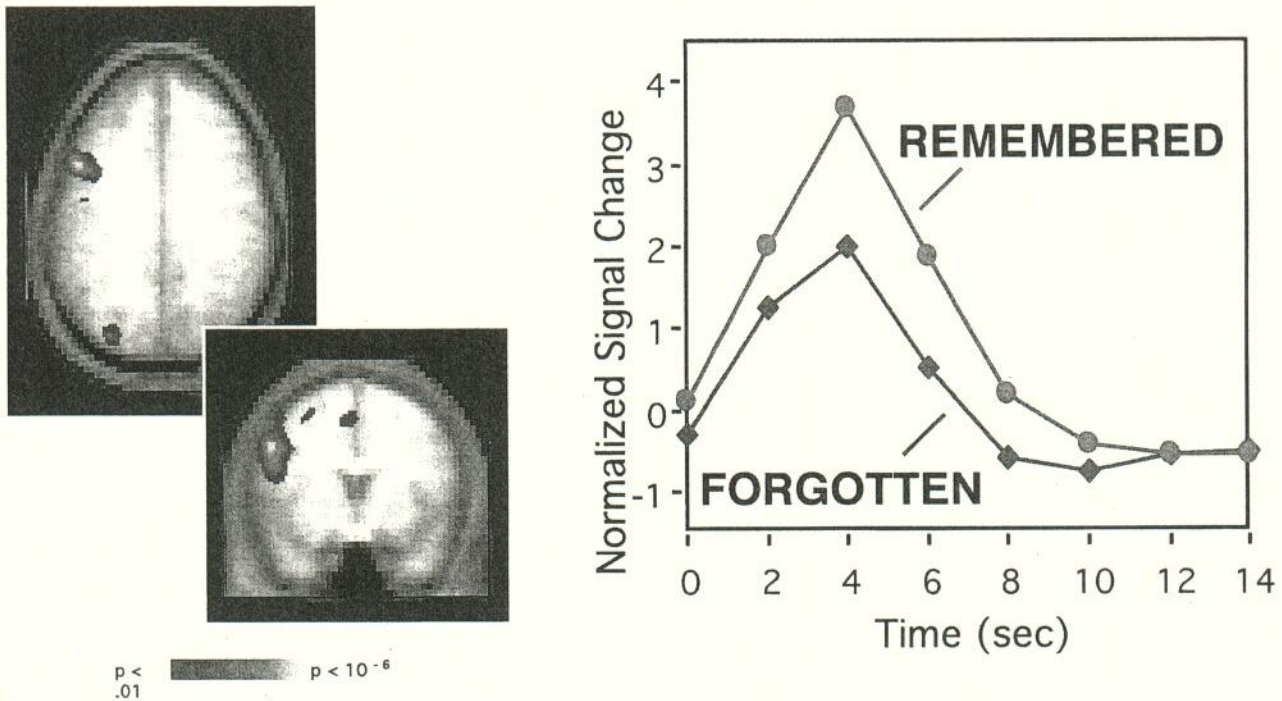


FIGURE 18.2. A schematic diagram presents representative results of activity in the left frontal cortex as a function of whether a word was subsequently remembered or forgotten. The brain images display the location of activity in the left frontal cortex that was predictive of later memory performance. The time course (in seconds) shows the evolving functional magnetic resonance imaging signal over a 14-s period after the onset of the word during encoding. (Adapted from Buckner RL, Logan JM. Frontal contributions to episodic memory encoding in the young and elderly (*in press*), with permission.)

between brain activity and behavior during episodic memory encoding. Of particular theoretical interest, the relationship between left frontal activity and subsequent memory for words has spanned a range of task contexts and even includes tasks involving episodic retrieval (37).

Domain Specificity of Prefrontal Cortex Contributions to Episodic Memory

As described above, activity within the frontal cortex is consistently associated with the encoding of verbal materials into episodic memory. However, the frontal cortex is not a homogeneous region. It contains numerous anatomically distinct areas as defined by changes in the distribution of cell types and density, interconnections to other brain areas, and physiologic properties (80). Multiple distinct areas have been identified in nonhuman primates and to a lesser extent in humans, based on such characteristics (13,24,40,140,147–149). Consistent with the hypothesis that the frontal cortex is a heterogeneous region, a growing body of research sug-

gests that the relationship between frontal cortex activity and episodic memory encoding is regionally specific. In particular, the existing research suggests at least two separate functional–anatomic dissociations in the frontal cortex that relate to episodic encoding. The first is dissociation between separate regions in the left frontal cortex and the second is dissociation between the left and right frontal cortex regions (35,135,136). Dissociation of left frontal cortex regions is discussed first.

Dissociation within Left Frontal Cortex Regions

In functional neuroimaging studies, the location of activity within the left frontal cortex associated with encoding has extended spatially from the dorsal extent of the inferior frontal gyrus near Brodmann areas (BA) 44 and 6 to more ventral and anterior regions, encompassing the classically defined Broca area and portions of the dorsolateral prefrontal cortex (near BA 45 and 47). Importantly, two distinct left frontal

cortex regions have dissociated themselves functionally in a number of neuroimaging studies. The first region is located near the dorsal extent of the inferior frontal gyrus (BA 44/6), and the second is located more ventrally and anteriorly (near BA 44/45/47). We often refer to these two regions as the dorsal and ventral regions, respectively. However, these labels should not be taken to reflect specific anatomic distinctions (such as a relationship with the dorsolateral prefrontal cortex). Other researchers have labeled these same or similar regions as posterior and anterior (100,193). The topmost panel of Figure 18.3, which is adapted from Buckner and Logan (33), displays the approximate locations of these regions,

which have been dissociated by considering their divergent behavior across multiple task comparisons (35,36,143).

Several researchers have speculated on the possible functional roles of these two regions. One hypothesis is that the BA 44/6 region may provide access to lower-level, more generally utilized forms of representation, perhaps based on phonology or lexical access and perhaps interacting with parietal regions also participating in phonologic access. Support for this possibility comes from the observation that elaborate verbal processing tasks almost universally activate this region independent of whether the task demands require access to phonology or more elaborate meaning-based

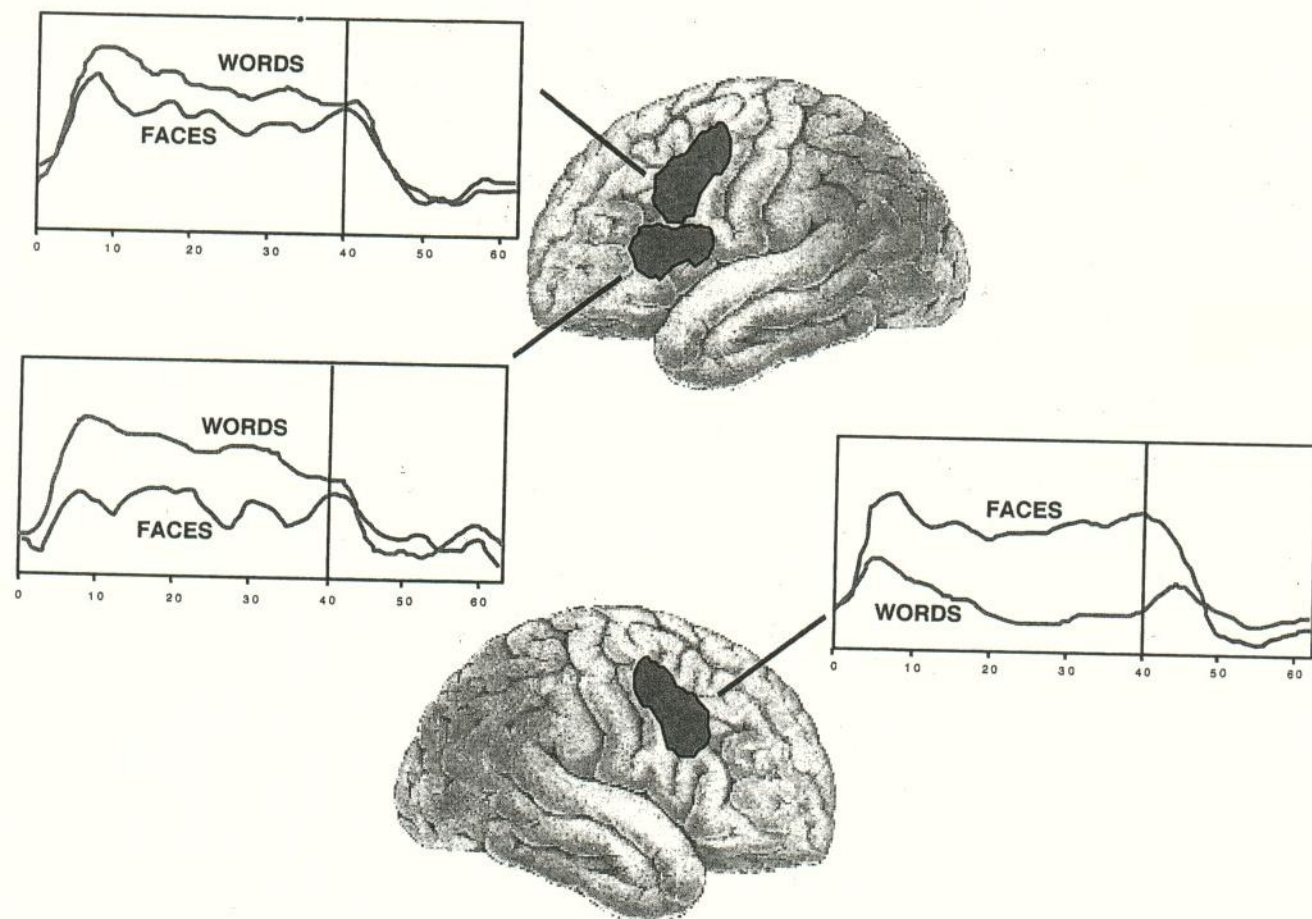


FIGURE 18.3. A schematic diagram heuristically represents the three frontal regions most consistently implicated in episodic memory encoding. Two separate left frontal regions, including Brodmann areas (BA) 44/6 and BA 44/6 regions, are plotted (top lateral view of brain). The third region is located in the right BA 44/6 (bottom lateral view of brain). Importantly, these regions dissociate functionally across encoding paradigms. One dissociation is shown by plotting the response over an encoding block for each region, separately for word and face encoding conditions. Each time course (in seconds) shows the evolving functional magnetic resonance imaging signal over a 40-s encoding epoch followed by a 24-s control period (encoding epoch ends and control period begins at the vertical line in each plot). Data were averaged over 272 separate encoding epochs. FACE and WORD time course data are plotted separately. Three important points are worth noting. First, there is increased involvement for WORD encoding in the left frontal regions and for FACE encoding in the right frontal regions. Second, within the left frontal cortex regions, the ventral (anterior) region is most selective for WORD encoding. Finally, for those regions showing little or no sustained responses (e.g., the word-encoding condition in the right frontal region), there is nonetheless a transient increase at the beginning and end of the epoch, perhaps reflecting an initial recruitment of the region. (See Color Figure 18.3 following page 526.)

processing (33). That is, to the extent that a word or wordlike representation is being extensively processed, the BA 44/6 region becomes active. Putatively nonverbal tasks have also activated (to a lesser degree) this BA 44/6 region, suggesting either an extremely general role of this frontal region in elaborate processing or the tendency of humans to incorporate verbal codes across almost all tasks. The BA 45/47 region may provide access to higher-level representations, perhaps based on meaning and related semantic associations, or selection among such representations (185). Evidence of this latter distinction comes from the finding that tasks requiring access to word meaning often activate BA 45/47 regions of the prefrontal cortex as well as the BA 44/6 regions, although it seems unlikely that the role of these more ventral regions will be exclusive to tasks tapping access to word meaning.

The relevance of the dissociation of these two regions to a discussion of episodic memory is that the BA 45/47 region appears to be more predictive of episodic encoding than the BA 44/6 region (33). In other words, in general, activity in the BA 45/47 region seems to be a better predictor of later memory performance. Considered from a functional perspective, this may directly relate to the possibility that the BA 45/47 region is required to access and/or manipulate representations associated with word meaning (36,100). As noted earlier, tasks requiring meaning-based elaboration are usually those most conducive to forming robust episodic memories.

Dissociation between the Left and Right Frontal Cortex Regions

The second prominent dissociation among frontal cortex regions relates to differences in encoding verbal and nonverbal materials. Cognitive theories have long suggested that memory formation relies on multiple kinds of information, with one important (albeit heuristic) distinction being between verbal and nonverbal codes. Behavioral studies have shown that a picture of an object, such as a lion, is more likely to be remembered than the presentation of the word "lion" (a finding known as the picture superiority effect). The implication is that pictures are associated with both nonverbal (image-based) and verbal codes, whereas words (particularly abstract words) are predominantly associated with just a verbal code (128,129). Moreover, patients with lateralized frontal lesions can show differences in memorization of different material types (115,155,199), suggesting code-specific regional specialization in the frontal cortex.

Several recent brain imaging studies have demonstrated that memorization of materials associated with different verbal and nonverbal codes can activate distinct regions of the left and right frontal cortex. As discussed above, the encoding of verbal materials such as words is associated with activation in specific left frontal cortex regions. By contrast, memorization of unfamiliar faces (101) and texture patterns (193), neither of which can be easily associated with a verbal label

strongly activates the right frontal cortex regions near the homologue to the left BA 44/6 frontal region. The locations of the left and right frontal cortex regions showing dissociation between material types can be seen in Figure 18.3. Several other studies using both positron emission tomography and fMRI have also noted similar effects (17,107,110). However, it should be noted that the pattern of right versus left frontal cortex activity as a function of material type likely reflects material *specialization* rather than material *specificity*. In other words, although verbal materials tend to elicit greater left than right frontal cortex activity and nonverbal materials tend to elicit greater right than left frontal cortex activity, this dissociation is not absolute. For example, research often finds activity in the left frontal cortex during the encoding of nonverbal materials, even when such information is not easily verbalizable (17,101,111).

Medial Temporal Cortex Contributions to Episodic Memory Encoding

As noted earlier, neuropsychological research on memory has long focused on the role of the medial temporal cortex in semantic and episodic memory, with a particular focus on the hippocampus and surrounding parahippocampal gyrus. Human functional neuroimaging studies have sometimes yielded results consistent with the involvement of the medial temporal cortex regions in episodic encoding. However, many studies that would be expected to show a relationship between medial temporal activity and episodic encoding have not, making this a particularly perplexing area of neuroimaging memory research. In terms of positive results, many of the same studies that have identified regions of the frontal cortex as active during episodic encoding have also demonstrated activity in the hippocampal and parahippocampal gyrus regions during both intentional and incidental episodic encoding (101,102,110,125,194). Further, studies that have examined neural activity at the time of encoding as a function of whether information is subsequently remembered or forgotten have also highlighted the importance of medial temporal activity in mediating the acquisition of new information (23,102,125,194). For example, Kirchoff et al. (102) found that activity in the hippocampus and parahippocampal gyrus at the time of encoding is greater for words subsequently remembered than for words subsequently forgotten. Recent work with depth electrodes implanted in humans undergoing surgery for epilepsy has provided further evidence of the specific involvement of the hippocampus in encoding, demonstrating that hippocampal activity at the time of encoding predicted subsequent memory for verbal stimuli (39).

As with work on the frontal cortex, research on medial temporal involvement in episodic memory encoding has provided some evidence of functional dissociation among medial temporal regions. One such proposed dissociation is similar to that proposed for the frontal cortex, with

dissociation between the right and left medial temporal regions as a function of material type.

Dissociation between the Right and Left Medial Temporal Cortex

Early work with lesion patients suggested the possibility that the left medial temporal cortex was relatively more involved in the encoding of verbal materials and the right medial temporal cortex was relatively more involved in the encoding of nonverbal materials (114). Several subsequent studies with patients with unilateral lesions to either the left or right medial temporal cortex provide support for this hypothesis. These studies have demonstrated that patients with unilateral left medial temporal lobe lesions are relatively more impaired on tests of verbal learning and memory (134,168,179), whereas patients with unilateral right medial temporal lobe lesions are relatively more impaired on tests requiring memory for items that are more difficult to verbalize, such as visuospatial materials (47,63,94,95,120,141,168,179,180). However, it should be emphasized that, as with the frontal cortex, the links between left temporal lobe lesions and verbal memory deficits and right medial temporal lobe lesions and nonverbal memory deficits are often relative rather than absolute. In other words, research has demonstrated that right medial temporal lobe lesions can impair verbal episodic memory, although perhaps not to the same extent as left medial temporal lobe lesions (57,165). Similarly, some studies have found that left medial temporal lobe lesions can impair nonverbal episodic memory, again although perhaps not to the same extent as right medial temporal lobe lesions (106).

Episodic Memory Retrieval

Prefrontal Cortex Contributions

As with episodic memory encoding, human episodic memory retrieval has been explored in many studies using a variety of materials, again including both verbal and nonverbal stimuli. Similar to studies of episodic memory, retrieval studies consistently engage the activity of a number of different prefrontal brain regions. In particular, the same BA 44/6 and BA 45/47 frontal regions activated by episodic memory encoding are activated by episodic memory retrieval, with similar lateralization as a function of material type (i.e., verbal vs. nonverbal) (17,111). Such results suggest that the processes supported by these regions of the frontal cortex are not specific to encoding per se, but rather reflect engaging the functions necessary for multiple aspects of memory performance. However, studies of episodic memory retrieval often activate regions of the frontal cortex not typically activated by studies targeting encoding. In particular, the more anterior and/or superior regions of the dorsolateral prefrontal cortex (BA 46/9) and regions of the frontal polar cortex (BA 10, with a tendency

to be right lateralized) are often activated by episodic memory retrieval, but not by episodic memory encoding (3,17,25,29,31,32,34,65,84,110,112,160,170,183,188,191).

Several different explanations have been put forth regarding the functional significance of activity in the frontal polar cortex during memory retrieval. For example, it has been suggested that frontal polar activation may represent the "set" or goal of attempting to retrieve past experiences, sometimes referred to as retrieval mode (30,113,121,188). Alternatively, it has also been suggested that the level of effort required during retrieval tasks modulate the level of activity in the frontal polar cortex (170). At a more specific level, others have suggested that activity in the frontal polar cortex may reflect successful recognition of items (112,159,160). Interestingly, the frontal polar cortex also appears to be reliably activated during planning, problem-solving, and reasoning tasks. For example, Baker et al. (11) observed frontal polar-prefrontal cortex activity in the Tower of London paradigm selectively under conditions that involved extensive planning. Such findings have led to the hypothesis that the frontal polar cortex may be more broadly involved in the monitoring of internally (vs. externally) generated information (42) or the maintenance of primary task goals while simultaneously allocating attention to subgoals (18,103). As should be clear by this discussion, despite the consistent findings of frontal polar activity in episodic memory retrieval, its precise role in human cognitive function is still unclear.

The findings of BA 46/9 activity during episodic memory retrieval has served to confirm findings from the neuropsychological literature highlighting the influence of damage in this region on episodic memory performance. However, individuals with circumscribed lesions of the frontal cortex are not grossly amnesic because they often score quite well on standardized measures of memory function (177). Nonetheless, their memory impairment can be detected on more sensitive tests of new learning. Further, damage to BA 46/9 does not selectively impair episodic memory but instead can impair a range of higher cognitive processes, including working memory, planning, and problem solving (176). In addition, the BA 46/9 regions activated in episodic memory retrieval tasks are often the same as those found in studies of working memory and planning (17,29). Taken together, such findings have led to the hypothesis that damage to BA 46/9 impairs episodic memory via an impact on the use of strategies that can enhance memory retrieval (176,177).

Consistent with this hypothesis, several studies have demonstrated that patients with damage to BA 46/9 are clearly impaired on episodic memory tasks requiring free recall of information (i.e., spontaneous generation of studied items) but are much less impaired (or even unimpaired) on tasks that simply require them to recognize whether an item was previously studied (177). In contrast, individuals with damage to the medial temporal cortex are often impaired on both recall and recognition measures (203). This difference in memory performance as a function of task

requirements has been explained in terms of the difference between the operation of familiarity versus explicit recollective processes. Familiarity refers to the ability to evaluate the contextual memory strength of an item and does not necessarily involve specific access to the episode in which the item was learned (90,187). In contrast, explicit recollection refers to the ability to access a specific memory of the learning episode and is thought to be much more influenced by the use of strategies at the time of retrieval as well as at the time of encoding (90,91,93,187). Thus, individuals with damage to BA 46/9 may be impaired on tasks requiring explicit recollection, in part because they have difficulties spontaneously using strategies that aid memory formation and retrieval (59,184). Patients with damage to BA 46/9 are also impaired on tasks that specifically require them to encode and/or retrieve the source of information (93) or the order in which the information was presented (177), deficits that may result from, or contribute to, impairment of explicit recollective processes.

In line with the hypothesis that BA 46/9 damage impairs strategy use, Gershberg and Shimamura (77) demonstrated that patients with damage to BA 46/9 are impaired in the ability to spontaneously use subjective organizational strategies and semantic clustering strategies during episodic memory tasks. Further, patients with lesions to BA 46/9 benefit from instruction in the use of strategies, both at the time of encoding and at the time of retrieval (77,89). Individuals with other neurologic and psychiatric disorders (i.e., schizophrenia, Parkinson disease, obsessive-compulsive disorder) also thought to involve frontal lobe dysfunction have been found to show similar patterns of strategic memory impairment (88,104,142,166,174). Recent fMRI work pro-

vides further support for the involvement of the dorsolateral prefrontal cortex in strategy use, demonstrating that activity in BA 46/9 can be elicited during encoding and retrieval if participants are engaging in strategies such as semantic clustering at the time of encoding (67,167).

Medial Temporal Cortex Contributions

As with the prefrontal cortex regions, studies of episodic memory retrieval often activate regions of the medial temporal cortex similar to those identified in studies of episodic memory encoding. However, a growing number of studies in this area has been devoted to trying to tease apart the specific contributions of different areas of the medial temporal lobe to memory formation and retrieval. As shown in Figure 18.4, the medial temporal cortex contains a number of anatomically separate regions that maintain hierarchical relationships with one another and receive convergent input from separate regions of the cortex. Lesions in many medial temporal lobe patients are relatively large, including both the hippocampus proper and surrounding entorhinal, perirhinal, and parahippocampal cortex, making it difficult to determine the specific roles that each of these regions plays in episodic memory. Nonetheless, some research has suggested that lesions restricted solely to the hippocampus in humans lead to moderate memory impairment, which primarily involves anterograde amnesia (inability to form new memories). More extensive damage that includes adjacent entorhinal and parahippocampal regions leads to much more severe impairment (203), which can include both anterograde and retrograde (loss of old memories) amnesia. Work with nonhuman primates provides a similar picture,

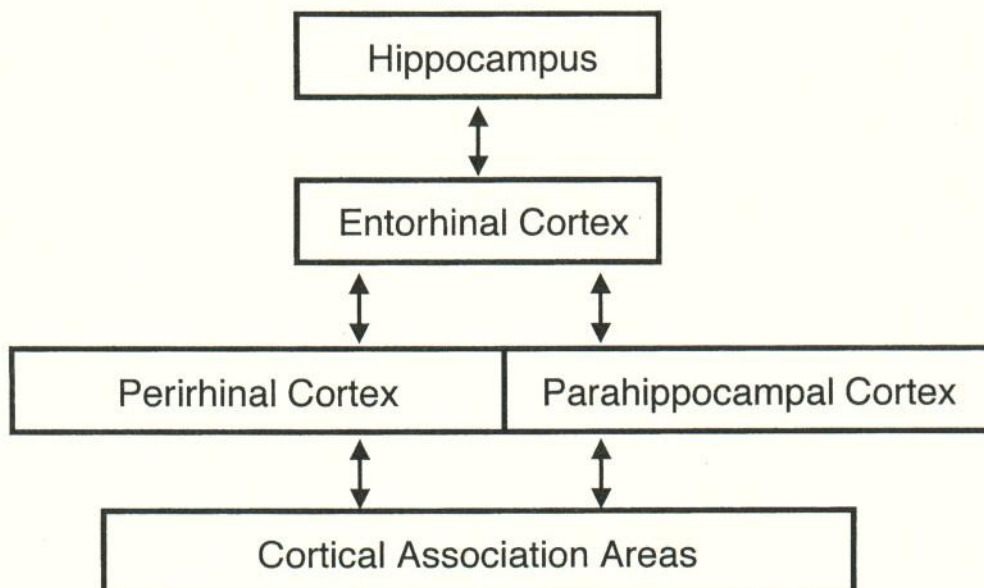


FIGURE 18.4. A schematic diagram outlines the major subdivisions of the medial temporal cortex and their connections with each other and with other brain regions.

demonstrating that lesions restricted to the hippocampus proper lead to moderate memory impairment, but lesions including the surrounding cortex lead to much more severe memory impairment (203). The anatomic organization of structures within the medial temporal cortex is such that one might expect such a specialized role for the hippocampus versus other medial temporal structures in memory function. At a simplified level, as shown in Figure 18.4, structures such as the parahippocampal and perirhinal cortex receive segregated inputs from distributed regions of the cortex and then send projections that converge on the hippocampus, resulting in a hierarchical organization of medial temporal structures.

As one means of making sense of the relationship between the extent of medial temporal cortex damage and the extent of memory impairment, Aggleton and Shaw (1) suggested that damage to the hippocampus proper leads to impairment of explicit recollection of episodic information but does not impair the use of more familiarity-based processes. In contrast, damage that includes the cortical structures surrounding the hippocampus (i.e., entorhinal cortex, parahippocampal gyrus) may impair both familiarity-based processing and conscious recollection. Aggleton and Shaw based this hypothesis on a review of 33 studies that examined recognition memory in patients with amnesia owing to a variety of different types of brain damage. Their review found that individuals whose lesions were restricted to the hippocampus had relatively intact recognition memory performance compared with recall performance. In contrast, individuals whose damage extended beyond the hippocampus tended to be impaired on recognition as well as recall performance. However, more recent work by Reed and Squire (154) calls this conclusion into question. They examined a somewhat larger group (six subjects compared with three in the study by Aggleton and Shaw) of individuals with lesions restricted to the hippocampus and found clear evidence of impairment of recognition and recall in these individuals. Further, research in the cognitive psychology domain has pointed out that one cannot necessarily equate performance of recall tasks with conscious recollection and performance of recognition tasks with familiarity, in that both recollection and familiarity can contribute to recognition memory task performance (90,201).

Despite this ongoing debate in the neuropsychology literature, recent event-related fMRI research provides evidence consistent with the hypothesis that the hippocampus may be particularly important for the explicit recollection. Eldridge et al. (58) examined neural activity at the time of memory retrieval as a function of whether the participants reported remembering or knowing that they had seen the item before. Participants were told to give a remember response (R) if their memory for the item was based on a distinct recollection of having seen the word at the time of encoding and to give a know response (K) if they had a feeling of familiarity that was not accompanied by explicit recollection of the learning episode (58). Activity in the left hippocampus was

significantly greater during retrieval of R responses compared with K responses, whereas activity to K responses did not differ from activity to correct rejections. A similar pattern was found in the right hippocampus, although the pattern was not as strong as in the left hippocampus. In contrast, regions of the parahippocampal gyrus were active in both R and K responses compared with correct rejections. These results provide support to the hypothesis that the hippocampus is more involved in explicit episodic memory recognition than in familiarity-based processes, but adjacent parahippocampal regions may also be important for familiarity-based processes. Clearly, however, further research is needed to tease apart the differential contributions of the different medial temporal regions to episodic memory function and its relationship with other forms of memory.

Relationship between Frontal and Medial Temporal Cortex Contributions to Episodic Memory

This review of the functional anatomy of episodic memory has attempted to summarize research demonstrating that multiple brain regions are critical for episodic memory function, including both the frontal and medial temporal cortex. Up to this point, however, we have not addressed the question of how the frontal cortex interacts with the medial temporal cortex to support episodic memory encoding and retrieval. We believe that the evidence to date suggests that the frontal cortex provides a source of information (an input or some form of modulatory influence) to medial temporal lobe structures (26,28,100,116) that serves to guide both memory formation and memory retrieval. This idea fits well with the hypothesis that medial temporal lobe structures (including the hippocampus and adjacent cortex) play a role in the integration and cohesion (binding) of incoming information to form memories (45,109,117,171). The frontal cortex may provide critical input to these medial temporal cortex structures, supplying the necessary "ingredients" that must be bound together to form an enduring episodic memory and providing important contextual cues that can help to facilitate memory retrieval. This idea is not new, and in fact other researchers using different methodologies have come to similar conclusions. For example, Squire (182) suggests that the "frontal cortex presumably performs its computations on many kinds of information, which are analyzed concurrently for other purposes by other regions of cortex. Frontal cortex allows information to be remembered in its appropriate context, that is, in the correct temporal coincident event. The medial temporal region then operates upon this information, allowing it to endure in the organized form it has achieved in neocortex." Moscovitch (117) suggests a related idea that the frontal lobes "are prototypical organization structures crucial for selecting and implementing encoding strategies that organize the input to the hippocampal component." Thus, both the frontal and medial temporal cortex regions are important to the formation of episodic memories, and both

the frontal and medial temporal cortex regions are critical for the successful retrieval of episodic memories, although potentially not for the same reasons.

WORKING MEMORY

As described earlier in this chapter, working memory is typically defined as the ability to temporarily maintain and manipulate information over a short period of time. Over time, the construct of working memory has evolved to encompass earlier definitions of short-term memory and to describe the interactions between processes that support the maintenance of information and those that operate on the maintained information. As with episodic memory, the construct of working memory contains several different subcomponents, each of which may map onto the function of different neural systems. For example, Baddeley's (8) model of working memory contains at least three different subcomponents, including two content-specific buffer systems and a central executive system, defined as a limited-capacity attention system that coordinates the activities of the phonologic loop and visuospatial scratch pad and operates on the contents of these systems. The buffer systems are thought to include a phonologic loop system that subserves the rehearsal of verbal information (similar to earlier concepts of verbal short-term memory) and a visuospatial scratch pad that supports nonverbal maintenance. As with episodic memory, working memory is clearly dependent on the coordinated activity of multiple brain regions. However, research from multiple domains, including neuropsychology, nonhuman primates, and human functional neuroimaging have implicated the frontal cortex as an area of the brain important for working memory function, although the precise functions supported by different regions of the prefrontal cortex and how they specifically contribute to working memory are an area of ongoing debate.

In particular, at least two potential means of functional dissociating regions of the frontal cortex involved in working memory have been proposed. One means of dissociation is based on process (storage/maintenance processes versus executive/manipulation processes) and is analogous to the distinction between the central executive and buffer systems. Another means of dissociation is based on the content of the information to be maintained (i.e., verbal, spatial, object), which can be thought of as analogous to a distinction between the phonologic loop and the visuospatial scratch pad.

Working Memory Process Dissociations in the Prefrontal Cortex

The hypothesis that regions of the prefrontal cortex, including the dorsolateral prefrontal cortex (BA 46/9) may be involved in the maintenance of information in working memory stems, in part, from research using nonhu-

man primate models of working memory. This literature has shown that circumscribed lesions in the region of the principal sulcus (argued to be nonhuman primate homologous of BA 9/46 in humans) can impair delayed response task performance in monkeys (69,73). Further, single-unit recordings demonstrate sustained neural firing in neurons in the principal sulcus, arcuate sulcus, and lateral convexity during the delay period of such delayed-response tasks in monkeys (68,70,71,74,124,200). Based on such findings, it has been argued that prefrontal cortex supports working memory by actively holding information "on-line" through maintained neural activity and that delay-period activity in the prefrontal cortex serves as the "cellular basis of working memory" (79). This view of prefrontal cortex involvement in working memory suggests that regions such as the dorsolateral prefrontal cortex support the processes carried out by the buffer system component of working memory rather than the central executive system, at least according to Baddeley's formulation.

In contrast, the neuropsychological literature on the influence of BA 46/9 lesions on working memory and executive control has emphasized the role of BA 46/9 in the central executive components of working memory rather than the mnemonic processes supported by the buffer systems (7,82,137). For example, a recent review by D'Esposito and Postle (50) found minimal evidence that lesions to BA 46/9 impair performance on span tasks (i.e., forward digit span, spatial span). Such tasks are thought to rely primarily on the function of the phonologic loop or the visuospatial scratch pad and to require little or no involvement of the central executive system. In contrast, they found more evidence that BA 46/9 lesions impaired performance on delayed-response tasks, particularly when the delay period was filled with distracting information. The inclusion of distraction during the delay period is likely to elicit executive functions such as interference control (41), and thus impairment in such tasks is consistent with the hypothesis that BA 46/9 plays a role in the executive components of working memory.

However, delayed-response tasks without distraction seem more dependent on maintenance functions as opposed to executive functions. Thus, the fact that individuals with BA 46/9 lesions can show impairment in such tasks leaves open the possibility that BA 46/9 regions do play a role in maintenance functions as well as executive control functions. Interestingly, individuals with neurologic or psychiatric disorders also thought to involve BA 46/9 show a similar pattern of performance on different working memory tasks. For example, patients with schizophrenia show relatively little impairment on span tasks (especially at subspan lengths) (161) but do show impairment on delayed-response tasks (with and without distraction) (131,132) as well as more complex working memory tasks (15,78).

The debate regarding which regions of the prefrontal cortex support maintenance versus executive control functions extends to the functional neuroimaging and nonhuman primate literature as well as the neuropsychology literature.

For example, Petrides (138,139) suggests that ventral (BA 44/45/47) and dorsal (BA 46/9) regions of the prefrontal cortex may differ in their relative involvement in maintenance versus executive control processes. Specifically, Petrides postulates a two-stage hierarchical model of lateral prefrontal cortex function. In Petrides' model, ventral (BA 44/45/47) regions of the prefrontal cortex perform simple executive- and maintenance-related processes from input from the posterior cortical regions as well as help to select and retrieve information from short- and long-term memory. In contrast, Petrides argues that the dorsal (BA 46/9) prefrontal cortex regions operate on input from these ventral regions and other cortical regions and are able to perform more complex executive operations, such as monitoring and manipulating the contents of information maintained in ventral regions. Animal lesion studies have provided some support for Petrides' model (138), and the human functional neuroimaging literature has also produced evidence of a similar division between ventral (BA 44/45/47) and dorsal prefrontal (BA 46/9) cortex regions (49,51,126,127,144).

In the human neuroimaging literature, the distinction between the operation of the buffer storage systems (phonologic loop, scratch pad) and the central executive system has been characterized as a distinction between maintenance and manipulation. A review by D'Esposito et al. (49) of neuroimaging studies using a variety of working memory tasks provided support for the hypothesis that a distinction between maintenance and manipulation corresponded to a division between BA 46/9 and BA 44/45/47 prefrontal cortex activity during working memory tasks. In this review, tasks thought to primarily involve maintenance (i.e., delayed-response type tasks) were associated with activation in BA 44/45/47 but not BA 46/9, whereas those involving both maintenance and manipulation (i.e., self-ordered pointing, "N-back" type tasks) activated both BA 44/45/47 and BA 46/9 regions of the prefrontal cortex. Of interest, the BA 44/45/47 regions associated with maintenance tasks in the working memory literature are essentially the same prefrontal cortex regions identified in studies of episodic memory encoding (both incidental and intentional) and retrieval. As such, although these regions may be engaged by the need to maintain information across time, their involvement in incidental episodic memory encoding paradigms suggests that the maintenance of information is not necessary to activate these regions, which is also consistent with the single-unit literature on monkeys.

Several event-related fMRI studies have since been conducted to test explicitly hypotheses regarding functional distinctions between BA 44/45/47 and BA 46/9 regions of the prefrontal cortex in working memory (21,51,144,162,163). Most of these studies have demonstrated that activity in BA 44/45/47 is reliably modulated by maintenance demands but not by manipulation demands [for an alternative view, see Braver and Speer (21)]. However, these studies suggest that BA 46/9 activity may be modulated by both maintenance

and manipulation demands. Additional research suggests that the degree to which dorsolateral prefrontal cortex activity is elicited by maintenance demands may depend on factors such as the amount of information to be maintained, i.e., high memory loads may necessitate the use of chunking strategies (21,66,76), and the nature of the information to be maintained, e.g., memory for contextual information may be more dependent on BA 46/9 function than memory for stimulus identity (14,19,20).

Working Memory Content Dissociations in the Prefrontal Cortex

The hypothesis that there may be dissociable working memory subsystems for different types of information stems from multiple sources. One source is behavioral studies demonstrating that in dual-task paradigms, verbal secondary tasks are much more likely to interfere with primary working memory tasks that are verbal rather than nonverbal, whereas nonverbal secondary tasks show the opposite pattern (8,119). Such results contribute to the hypothesis that there may be separate verbal and nonverbal subsystems within working memory. Another source of support comes from animal neurophysiology research, suggesting regional specificity in delay-related neuronal activity in the prefrontal cortex as a function of stimulus content. Goldman-Rakic (79,80) has made the strongest arguments for this type of material-specific organization scheme in the prefrontal cortex based on data from single-cell recordings in nonhuman primates. For example, Goldman-Rakic and colleagues (200) showed that neurons in the ventral prefrontal cortex demonstrate greater sensitivity to object identity than to spatial location, whereas neurons in the dorsolateral prefrontal cortex show greater sensitivity to spatial location than to object identity (200). Further, even within the dorsolateral prefrontal cortex, Goldman-Rakic and colleagues (69) demonstrated that focal lesions can lead to "memory scotomas" causing selective impairment of delayed-response performance with specific spatial locations. Based on such data, Goldman-Rakic (81) postulates a multiple-domain model in which object and spatial dimensions of working memory are one possible functional subdivision found within the prefrontal cortex. This hypothesis has appeal in that it parallels a similar distinction made regarding dorsal and ventral processing streams in posterior brain regions, referred to as the "what" (ventral stream, object identity) and "where" (dorsal stream, spatial location) pathways (189).

Such hypotheses regarding material-specific subdivisions within working memory have inspired a large body of research examining such distinctions in humans. This research fairly consistently demonstrates evidence of material-type specialization related to working memory function in the ventrolateral (BA 44/45/47) regions of the prefrontal cortex. In particular, multiple studies have demonstrated greater activity in the left BA 44/45/47 prefrontal regions during

verbal working memory tasks but greater activity in the right BA 44/45/47 prefrontal regions during visuospatial working memory tasks (17,178). This body of findings was recently reviewed by D'Esposito et al., who concluded that the research to date provides consistent support for material-specialized activity in the BA 44/45/47 regions of the prefrontal cortex during working memory performance (49). As hinted at above, these regions showing material-sensitive activity during the performance of working memory tasks are similar to those showing material sensitivity during the performance of episodic memory encoding and retrieval tasks (17), again suggesting that the cognitive functions supported by these regions are not selective to any one memory domain but rather may provide more general processing resources that are adapted to multiple memory forms.

Despite the evidence of material-sensitive activation patterns in the BA 44/45/47 regions of the prefrontal cortex, there has been relatively little evidence of differences in the location of BA 9/46 activity during working memory performance as a function of material type (49,123,145). Instead, numerous studies have suggested that similar regions of BA 46/9 are activated by verbal, spatial, and object working memory tasks, with activity typically either bilateral or right lateralized (17,38,49). Consistent with the results from neuroimaging studies, work in patients with lesions to BA 46/9 suggests that lesions to either the right or left hemisphere can impair performance of visuospatial working memory tasks (12). Recent work in nonhuman primates also calls into question the issue of material specificity in BA 46/9. Specifically, Rao et al. (150) showed that neuronal activity in the dorsolateral and ventrolateral prefrontal cortex can be sensitive to both spatial and object characteristics during the performance of working memory tasks, if successful performance of the task requires attention to both spatial and object characteristics of the stimulus. In many ways, a lack of material-selective processing in BA 46/9 is consistent with a role for this region in more executive or control components of working memory because such processes are likely to be engaged by many or all types of material (i.e., words, faces, objects, spatial locations).

In summary, the literature on prefrontal cortex involvement in working memory function suggests that BA 44/45/47 regions are involved in the maintenance of information in working memory and demonstrate patterns of material-sensitive activity that parallel those found during performance of episodic memory tasks. In contrast, BA 46/9 regions show relatively little evidence of material-sensitive patterns of activity and appear to be more involved in the executive components of working memory. The involvement of BA 46/9 regions in executive components of working memory is consistent with the evidence demonstrating that these same regions are also important for mediating strategic aspects of episodic memory processing. Nonetheless, further research is clearly needed to isolate the specific cognitive functions supported by BA 46/9 regions of the prefrontal

cortex and to determine what principles guide functional organization in these regions if material type is not the determining factor.

Nonfrontal Cortex Contributions to Working Memory

The vast majority of research on the correlates of working memory function has focused on the role of the prefrontal cortex. However, as with episodic memory, neuropsychological research and functional neuroimaging studies have demonstrated that regions outside the prefrontal cortex also play important roles in working memory, including the basal ganglia, thalamus, and parietal cortex. For example, almost all neuroimaging studies of working memory find activation in the parietal cortex, both with verbal and nonverbal materials.

One hypothesis about the role of the parietal cortex in working memory is that the parietal cortex in the language-dominant hemisphere (typically the left hemisphere in the region of the supramarginal and angular gyri) is the anatomic locus of the phonologic storage component of the phonologic loop (16,96,133) as opposed to rehearsal components (associated more with the inferior frontal cortex) (5,6). As such, it seems possible that the frontal regions near BA 6 may interact with the parietal cortex to subserve Baddeley's phonologic loop. Further, it has also been argued that the right parietal cortex may play a role in visuospatial rehearsal processes via its involvement in visual-selective attention (6). Consistent with these hypotheses, neuropsychological research has shown that lesions of the left inferior parietal cortex can impair working memory tasks that tap phonologic storage and/or rehearsal (span performance, in particular) (164,175,190,196,197). In contrast, lesions of the right inferior parietal cortex can impair nonverbal working memory tasks that tap visuospatial storage and/or rehearsal (56,83).

SEMANTIC MEMORY

As described at the beginning of the chapter, semantic memory refers to an individual's general knowledge about the world, including facts, the meanings of words and concepts, and the relationships among concepts and ideas. Some theorists have argued that the critical difference between semantic memory and episodic memory is that the semantic knowledge is not necessarily tied to any specific learning experience, as it often is in episodic memory (186). As with episodic memory, semantic memory impairment is often associated with lesions of the medial temporal cortex, in that damage to the hippocampal formation can lead to impairment of the ability to learn new semantic as well as new episodic information. However, selective impairment of the retrieval of already formed semantic memories, compared with episodic memory, is typically *not* associated with

selective damage to the hippocampus *per se* but rather to other regions of the temporal cortex. Warrington (195,198) presented the first research on individuals who demonstrate selective semantic memory impairment (i.e., confrontation naming, word-picture matching, tasks requiring individuals to access knowledge about the attributes and use of specific objects) in the context of relatively preserved functions in other areas of language and cognition. More recently, disorders of this type have been referred to as semantic dementia (181). A clear assessment of the intactness of episodic memory is often difficult in these individuals, in part because the semantic impairment makes it difficult for them to process words and pictures appropriately. However, some have suggested that there is evidence of preserved autobiographical memory in such individuals (86). Such selective impairment of semantic memory has been found in individuals who have recovered from herpes encephalitis (198) and in individuals with Pick disease (61). Individuals with late-stage Alzheimer disease can also demonstrate impairment of semantic memory, but these individuals also clearly show impairments of many other aspects of memory, including episodic and working memory.

Interestingly, several reports suggest the presence of category-specific semantic memory impairment in some individuals, such as more impairment in naming living things than nonliving things (85). Such findings have been hypothesized to reflect separate memory systems/mechanisms for the recognition of living versus nonliving things (62). Consistent with this hypothesis, functional neuroimaging studies have revealed differences in the anatomic location of brain activity during the naming of pictures of living things (e.g., animals) versus nonliving things (e.g., tools) (108). For example, naming pictures of animals was found to produce greater activation in the occipital cortex, whereas naming tools produced greater activation in the left premotor and left medial temporal cortex (108). Somewhat similar, although not identical, results have been found by Damasio et al. (53). Retrieval of other types of semantic information (i.e., color information, action information, face) has also been found to elicit activity in neuroanatomically distinct regions of the temporal cortex, often in regions close to the temporal cortex regions associated with the initial perception of such attributes (172).

The data on differential deficits in semantic knowledge about living versus nonliving objects, combined with the functional neuroimaging data suggesting differences across domains of semantic knowledge, have been used to support the hypothesis that semantic information about different categories of objects and events is stored in different cortical regions. However, this view has been criticized on the grounds that putative dissociations in the ability to name living versus nonliving objects may simply reflect different degrees of naming difficulty, with the stimulus materials often used to assess living objects being more difficult than those used to assess nonliving objects (i.e., lower frequency

words, less familiar objects, more visually complex) (72). Farah et al. (62) argue against this view and provide support for the existence of a living/nonliving dissociation with stimulus materials of equal difficulty. Such findings, together with the functional neuroimaging research described above, suggest that there may be important differences in the location and/or functions of the brain regions supporting semantic memory for different types of information. Further research will be needed to resolve these debates.

SUMMARY

The explosion of functional neuroimaging research in humans over the past 20 years, combined with neuropsychological and nonhuman primate research, has vastly increased the amount of information that we have about the relationships between different aspects of memory function and their associated neurobiologic systems. As such, we have a growing understanding of the expected similarities and differences in the profiles of memory impairment demonstrated by individuals with lesions to different areas of the human brain. At the same time, research on the functional anatomy of memory continues to demonstrate that there are few, if any, one-to-one mappings between our current concepts of memory forms and the function of any particular brain region. Instead, it is clear that many putatively different subcomponents of memory share common processing elements and are supported by the overlapping brain regions. Nonetheless, the recognition that humans have access to multiple forms of memory has helped to make sense of the varying profiles of spared and intact cognitive function that can occur with diseases and lesions that can influence the human brain.

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