Chapter 22

AMNESIA II: COGNITIVE NEUROPSYCHOLOGICAL ISSUES

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Research in cognitive neuroscience has inspired the view that distinct neural systems are differentially involved in various aspects of memory. While most or all information processing systems in the brain are capable of using past information to influence current behavior, there is a great deal of functional heterogeneity in the aspects of learning and memory that are supported by different neural mechanisms. This chapter provides an overview of cognitive neuroscience research on the principal brain mechanisms of memory. We start with a discussion of research that has attempted to evaluate the contribution of the medial temporal lobe and related structures to memory by investigating the amnesic syndrome. This research has inspired new perspectives on the storage and retrieval of information in long-term memory. Findings of preserved learning and memory in amnesic patients have suggested that some brain mechanisms support forms of memory that can operate unconsciously (implicit memory) and have also pointed toward distinct short-term forms of memory (working memory). Finally, the contribution of the prefrontal cortex to long-term memory and working memory are discussed.

AMNESIA AND MEDIAL TEMPORAL LOBE FUNCTION: COGNITIVE NEUROPSYCHOLOGICAL PERSPECTIVES

Patients with organic amnesia show profound learning and memory impairments that are typically attributable to medial temporal lobe and/or diencephalic damage (see Chap. 21 for a review of these impairments). Research investigating the functional deficit(s) underlying organic amnesia have been strongly influenced by theories of normal learning and memory. Models of human memory that posit a distinction between short- and long-term memory generally have been supported by the finding that amnesic patients show normal retention of small amounts of information (about seven items) across short temporal durations (less than about 30 s). As discussed below, short-term or working memory is supported by neurocognitive processes that are separable from long-term forms of retention. We now consider the component processes of long-term retention that may be compromised in organic amnesia.

Cognitive psychologists generally distinguish between three different information processing stages of memory: encoding, storage, and retrieval. The integrity of each of these stages has been investigated in order to understand the memory impairment resulting from organic amnesia. The observation that amnesic patients can show normal levels of memory when certain retrieval cues are provided (e.g., a three-letter word stem, *tru*, to cue memory for *truck*) led to the hypothesis that amnesia results from a retrieval deficit. Because interference, or competition among similar memories, is considered to be a primary determinant of retrieval failure in normal subjects, retrieval-deficit theories predicted abnormally high levels of interference in amnesic patients. Contrary to
nesia is typically associated with some retrograde memory loss. 

Retrieval-deficit theories of amnesia suffered from another, more fundamental flaw that does not relate to interference. The ability to retrieve information encountered prior to the onset of amnesia can remain intact (especially if the information was learned long before the onset of amnesia) despite profound impairments in retaining new information (see Chap. 21). That is, anterograde amnesia can exist without retrograde amnesia. If amnesia involved only a general retrieval deficit, it should affect the retrieval of old and new information equally. The separability of anterograde and retrograde amnesia suggests that the amnesic deficit is likely attributable (at least in part) to an impairment at the time of learning. For this reason among others, encoding deficit theories of amnesia have been proposed.

The levels-of-processing framework has greatly influenced cognitive psychologists’ ideas about the manner in which information is encoded into memory. Simply stated, this framework describes the fact that information is remembered more accurately when semantic rather than superficial aspects of stimuli are encoded. Thus, amnesic patients’ memory impairments have been hypothesized to reflect a deficit in encoding to-be-remembered information at a semantic level. Semantic coding deficit theories received initial support when Korsakoff’s amnesics failed to show a normal levels-of-processing effect, but subsequent studies have found normal levels-of-processing effects with other amnesic patients. Other studies suggested that amnesic patients did not spontaneously use semantic information to organize and encode information in memory but that they could encode semantic aspects of stimuli when properly instructed. Ultimately, semantic coding deficits cannot entirely explain the memory deficit of patients with anterograde amnesia. Besides the evidence that amnesics can properly encode semantic attributes, any theory that focuses purely on encoding processes has difficulty explaining the differential effectiveness of different retrieval cues or the fact that anterograde amnesia is typically associated with some retrograde memory loss.

Cognitive theories of encoding (e.g., levels-of-processing) and retrieval (e.g., interference theory) have generally been unsuccessful in explaining the amnesic syndrome. Storage-deficit theories, rather than being directly borrowed from cognitive psychology, exemplify how neuropsychological evidence has influenced the evolution of psychological theories. In particular, cognitive neuroscience research on amnesia has revolutionized our ideas about the storage process known as consolidation. Consolidation was originally conceptualized as the process by which information is transferred from short- to long-term memory. More recent theories posit that consolidation is a longer-term process by which memories are integrated with existing knowledge over a time course that lasts from minutes to years. According to consolidation theories, memories initially depend on an interaction between the temporal lobe/diencephalon and the cerebral cortex. Over time, the learned representations become integrated with other knowledge in the cerebral cortex and no longer depend on the medial temporal lobe or diencephalon. Evidence for this view is derived from the observation that (1) retrograde and anterograde amnesia are typically correlated and (2) retrograde amnesia follows a temporal gradient. The temporal gradient of retrograde amnesia refers to the finding that retrograde amnesia is typically most severe for information that was encountered immediately prior to the onset of amnesia but is progressively less severe for remote events (see Chap. 21). According to consolidation theories, remote memories have already been completely consolidated with information in the cerebral cortex, so they are no longer dependent on the brain regions affected in amnesia (i.e., medial temporal lobes and/or diencephalon). More recent memories, for which retrograde amnesia is most severe, have not been consolidated, so they are most likely to be lost upon the onset of amnesia.

Another proposed function of the medial temporal lobes—related to consolidation—is the binding of distinct memory attributes that are represented in distributed cortical areas. By this
view, different stimulus attributes are ultimately represented and stored in dedicated cortical areas: visual features in occipitotemporal cortex, spatial information in parietal cortex, auditory information in superior temporal cortex, and so on. Medial temporal lobe mechanisms interact with these cortical representations to bind them into a coherent memory of the remembered episode. Through consolidation, these cortical representations become directly associated with each other and are no longer dependent upon medial temporal lobe binding.

The previously discussed theories of the amnesic deficit can be collectively referred to as process theories because they try to relate medial temporal lobe function to a particular memory process (e.g., encoding, binding, consolidation, retrieval). Another general class of theories, content theories, have posited that the memory deficits of amnesic patients involve only certain types of information. One example of such a theory posits that amnesics’ memory for information about individual items is normal, but amnesics’ deficit is specific to contextual or associative information. Other theories hold that the performance of amnesic patients is impaired on tests that require conscious recollection of a previous episode (“explicit memory”) but is spared on tasks in which memory influences behavior without conscious recollection (“implicit memory”). As will be seen, these dichotomies (item information versus contextual/associative information, explicit versus implicit) are orthogonal to the process theories, and it is reasonable to combine the two approaches. That is, if amnesics’ memory deficits are confined to associative information, this associative-memory deficit could be attributable to a certain stage of information processing. Furthermore, these content dichotomies are not mutually exclusive, so, for example, it is important to consider implicit memory for item information as well as implicit memory for associative information.

Context-memory deficit hypotheses suggest that memory for individual stimuli is spared by organic amnesia, but memory for contextual information (e.g., time, place, and so on) within the learning episode is impaired. A related idea holds that damage to medial temporal lobe structures has little effect on memory for individual stimuli but impairs the ability to remember complex associative or relational information about multiple stimuli. A central issue in evaluating context-memory deficit theories is whether or not amnesics’ recognition abilities (i.e., the ability to discriminate studied from nonstudied items) is relatively spared in comparison with free or cued recall. The importance of recall versus recognition performance is derived from the fact that recall is typically more context-dependent than recognition. Some studies have found that recognition is spared relative to recall in patients with organic amnesia but others have shown that recall and recognition are similarly impaired. Even if amnesics do show a greater deficit on recognition than recall, context-deficit theories have difficulty explaining the fact that recognition—though better than recall—is not normal in amnesic patients. Such an explanation requires more detailed theories of the conditions in which context-memory influences item recognition.

There is an important relationship between content theories positing an amnesic deficit in associative/contextual memory and process theories positing that the medial temporal lobes act as a binding mechanism. The ability to remember associations between stimuli or to remember the episodic context in which a stimulus was encountered clearly depends on the associative binding of information in memory. Theories that posit a medial temporal lobe (and diencephalic) contribution to consolidation and binding appear to be very promising. Below, we discuss the capacity for other types of learning and memory that do not depend on these mechanisms.

**IMPLICIT MEMORY**

In considering evidence for retrieval-deficit theories of amnesia, we discussed the finding that amnesic patients’ memory can appear normal when tested with appropriate cues like word stems. Graf and coworkers showed that the instructions given
to subjects may be just as important as the physical retrieval cue in determining how the memory performance of amnesic patients will compare to that of control subjects. When subjects were asked to intentionally recall a studied word that completes the stem (a direct test of explicit memory), control subjects outperformed amnesic patients. However, when subjects were simply asked to respond with the first correct completion that came to mind (an indirect test of implicit memory), amnesic and control subjects performed equivalently. Both groups of subjects showed superior completion rates for studied compared to nonstudied words (this effect is typically called “priming”), so it is clear that both groups were being influenced by memory for the studied words. This finding of spared priming on implicit tasks has been well replicated (for reviews, see Refs. 18 and 19). Thus, implicit memory does not seem to depend on the medial temporal and diencephalic brain areas that are damaged in organic amnesia.

Implicit memory is observed in tasks in which previous experience can influence behavior in the absence of conscious recollection (for review, see Ref. 20). Research on normal subjects has distinguished between two types of implicit memory tasks: (1) perceptual tasks in which the retrieval cue is perceptually related to the target item (e.g., stem completion, _true——_) and (2) conceptual tasks in which the retrieval cue is conceptually related to the target item (e.g., category exemplar generation, _vehicle—_). We will focus on perceptual forms of priming because more is known about the underlying brain mechanisms. In general, performance on perceptual implicit memory tasks is unaffected by semantic variables that greatly influence explicit memory. For example, in our discussion of encoding theories of amnesia, we noted that explicit memory normally benefits from semantic encoding compared to an encoding strategy that emphasizes physical characteristics of the studied stimulus. In contrast, perceptual priming shows little benefit from semantic encoding. Unlike explicit memory, perceptual priming is sensitive to the perceptual compatibility between study and test conditions. On a visual stem completion task, for example, priming is superior when the study list is presented visually rather than auditorally.

The semantic independence and perceptual sensitivity of implicit memory has suggested that it reflects the influence of previous experience on presemantic brain mechanisms that are normally involved in perception. Cognitive neuroscience studies of perception indicate that different cortical areas are involved in the perception of different kinds of stimuli, such as visual words, auditory words, or visual objects (see Chaps. 6, 15, and 18). For example, evidence from neuropsychology and neuroimaging has converged on the idea that perception of visual words relies on mechanisms in occipitotemporal cortex.

Schacter has suggested that implicit memory is driven by modality-specific perceptual systems. This view has been supported by positron emission tomography (PET; see Chap. 3) studies of the functional anatomy of stem-completion priming. Activation by PET in bilateral occipitotemporal regions was stronger when word stems were completed with nonstudied words compared to previously studied words. This is consistent with the idea that priming reflects an influence of previous experience on the mechanisms that underlie visual word perception such that word perception is made easier by previously studying the word. Other PET evidence suggests that similar conclusions apply in the domain of visual object processing.

Converging evidence for a contribution of visual cortical areas to implicit memory has been provided by a study of memory and priming in a patient, M. S., who had most of his right occipital lobe removed in order to alleviate intractable epilepsy. M. S. showed normal explicit memory on a variety of tests but impaired perceptual priming on word-stem completion and word-identification tasks. Further evidence for the visuoperceptual nature of his priming impairment was obtained by demonstrating normal priming when words were studied auditorily rather than visually and normal priming on a conceptual test of implicit memory.

In summary, neuropsychological and neuroimaging studies of visual word priming have
strongly implicated visual perceptual mechanisms in occipitotemporal cortex. Other evidence suggests that distinct perceptual mechanisms contribute to implicit memory for auditory words and visual objects. Similarly, brain areas controlling perceptuomotor coordination can implicitly learn information that helps to guide subsequent behavior (often referred to as “procedural learning”). These results support the general conclusion that implicit learning and memory reflect the effects of experience on the brain mechanisms that normally support perception and guide behavior. These same information processing mechanisms likely form the cortical storage sites that are bound by medial temporal lobe mechanisms to support explicit recollection of coherent memory episodes. In this light, it is interesting to note that memory for novel associations between multiple stimuli cannot be implicitly retrieved by amnesic patients except under conditions of very extensive training. This is consistent with the notion that conscious recollection and associative binding are dependent on the medial temporal lobe, but unbound cortical memories can still have an unconscious influence on behavior.

**PREFRONTAL CONTRIBUTIONS TO LONG-TERM MEMORY**

Neuropsychological studies of patients with frontal lobe damage have traditionally suggested that prefrontal cortex plays only a subsidiary role in normal memory functioning. This view has been derived from the observation that patients with frontal lesions typically show memory deficits only for certain types of information (e.g., source memory and memory for temporal context). The term source amnesia refers to cases in which a person can normally remember some previously learned information yet cannot remember the source of that information (where or when it was learned or who taught it). For example, Janowsky and colleagues taught subjects some new trivia facts (e.g., “The name of the dog on the Cracker Jack box is Bingo”). Patients with frontal lobe lesions were able to answer correctly questions based on the newly learned information (e.g., “What is the name of the dog on the Cracker Jack box?”) as well as control subjects, yet they showed an impaired ability to remember where they learned the information or when they had most recently encountered it. Impaired memory for temporal information has been demonstrated in experiments in which subjects are asked to remember the order in which items appeared on a studied list. Patients with frontal lobe lesions can demonstrate normal recognition memory but impaired temporal memory for the same stimuli.

Other evidence suggests that the prefrontal cortex is more intimately involved with normal memory functioning than merely supporting memory for circumscribed types of information such as temporal or source memory. Explicit memory studies using PET have found that activity in the right prefrontal cortex is consistently associated with the retrieval of information from memory (for review, see Ref. 33). These results suggest that prefrontal mechanisms may play a more central role in memory retrieval than previously believed.

Recent neuropsychological work has sought to better understand the contribution of prefrontal cortex to memory retrieval. Shimamura and colleagues have suggested that patients with frontal lobe lesions have difficulty disregarding or inhibiting irrelevant information. Shimamura and coworkers had subjects learn consecutive lists with competing paired associates (e.g., lionhunter in list 1 and lion-circus in list 2). Patients with frontal lobe lesions showed impaired memory when asked to recall the list 2 associations (lion-?) because of high levels of interference from the pairs in list 1. Unlike patients with the classic amnesic syndrome, patients with memory problems associated with frontal lobe damage often confabulate. Confabulation can be characterized as “honest lying,” in which patients present inaccurate and sometimes bizarre “memories” of previous events. Other patients with frontal lobe lesions, who do not spontaneously confabulate about their life experiences, exhibit an intriguing form of false memory on recognition tests. For example,
one patient with a right frontal lesion, B.G., has been tested in a large number of recognition memory experiments in our laboratory. He classifies nonstudied test items as “studied” at a rate that consistently exceeds the false recognition of control subjects. Furthermore, like other frontal patients exhibiting false recognition, he shows an abnormally high degree of confidence in the accuracy of his false memories.

One experiment was particularly informative for understanding the possible basis of B.G.’s false recognition and shedding some light on prefrontal contributions to memory (Ref. 39, experiment 7). B.G. studied a list of pictures that were selected from a limited number of categories (e.g., furniture, tools, and so on). In the recognition test, nonstudied pictures were either members of the studied categories or not members of categories that were tested (e.g., animals). Figure 22-1 shows the percentage of times that subjects called pictures “studied” in each condition. The error bars represent the range of eight control subjects. As seen in Fig. 22-1, B. G. shows a heightened sensitivity to the category membership of the nonstudied pictures. His false recognition rate was near normal when nonstudied pictures were taken from nonstudied categories but was drastically higher when they were taken from studied categories. This suggests that B. G. may be more reliant on a general match between study-list characteristics and test items than are normal subjects. Hence, his right frontal lesion may make him less able to retrieve item-specific information from memory and force him to depend more on general representations of the target episode. This pattern might also be interpreted within Shimamura’s theory that patients with frontal lobe lesions have difficulty suppressing interfering information—the categorical structure of the list may indiscriminately bring all members of the studied categories to mind, but he may be unable to pick out the pictures that were actually studied.

Other theories of prefrontal contributions to memory emphasize its general involvement in the high-level control of cognition and behavior. Such high-level, or executive, control processes are thought to guide memory functioning just as they guide other cognitive processes. Executive processes may strategically guide memory search processes, or they may be used to monitor the information that is retrieved from memory and verify its accuracy. Either of these proposals could potentially account for the false recognition pattern exhibited by patient B. G. B.G. may falsely recognize pictures that are related to actually studied pictures because he fails to search for memory attributes that will successfully discriminate between studied and nonstudied pictures. In addition, B. G. may have a deficit in verifying the information that is retrieved from memory in order to avoid false recognition.
WORKING MEMORY

Baddeley\textsuperscript{43,44} has hypothesized that an executive control process (the "central executive") forms the centerpiece of a tripartite working memory system that allows for the temporary maintenance and manipulation of information. In addition to the central executive (similar to the frontal executive processes discussed above), two modality-specific slave systems—the "phonological loop" and "visuospatial scratch pad"—are hypothesized to temporarily store and manipulate speech-based and visuospatial information respectively. Working memory is typically normal in patients with the amnesic syndrome discussed at the opening of this chapter, so it is considered to be independent from the medial temporal lobe and diencephalic memory system that is required for normal long-term memory. In addition, phonologic and visuospatial working memory appear to be functionally and neuroanatomically distinct, because brain-injured patients with working memory deficits have shown impairments for either speech-based or visuospatial information but never both. In general, these modality-specific subsystems appear to operate in conjunction with the brain mechanisms that are involved in the perception of speech and visuospatial information.

A number of patients have been described who show impaired verbal short-term memory but normal long-term memory (for review, see Ref. 45). The possibility of normal long-term with impaired short-term memory contradicted early information-processing models of memory, which supposed that normal short-term memory processing is a necessary antecedent of normal long-term memory. Such patients may have a phonologic loop impairment, and their lesions are typically near the left supramarginal gyrus (inferior parietal lobe). A recent PET study has also found activation of the supramarginal gyrus in a phonologic working memory task.\textsuperscript{46}

Other neuropsychological patients appear to have deficits in visuospatial working memory but preserved verbal working memory (for review, see Ref. 47). The anatomic origins of these impairments have not been well localized beyond the predominance of right-hemispheric damage. Better information about the functional anatomy of visuospatial working memory has been provided by a PET study of visuospatial working memory.\textsuperscript{48} Consistent with the existing neuropsychological evidence, activity related to visuospatial working memory was confined to the right-hemispheric regions, including prefrontal, premotor, parietal, and occipital cortices. A prefrontal contribution to spatial working memory has also been suggested by single-unit recording in monkeys performing a task that requires short-term memory of visuospatial stimuli.\textsuperscript{49} Within the framework of Baddeley’s working memory model, it is unclear whether this prefrontal activity reflects the central executive or the visuospatial scratch pad (see Chap. 25 for further discussion of the choice between central executive and working memory accounts of prefrontal function). Given the well-established role of the parietal and occipital cortices in processing spatial and visual information, it seems clear that activity in these areas uniquely reflects the maintenance of visuospatial information—much like the hypothesized visuospatial scratch pad.

SUMMARY

Cognitive neuroscience research has inspired the view that memory is supported by multiple neural systems. Research on implicit memory and perceptual priming suggests that cortical information-processing modules are capable of some rudimentary forms of learning and memory. Experience shapes the operation of these perceptual mechanisms in a manner that can influence subsequent behavior without conscious recollection. The medial temporal lobe acts to bind information from these diverse cortical modules into a coherent memory episode that can be consciously recollected. Over time, these bound representations become consolidated into a distributed memory trace that is integrated with other information in long-term memory and is no longer dependent upon medial temporal lobe binding. Mechanisms of the prefrontal cortex interact with these core memory mechanisms in a manner that is just beginning to
be elucidated. Prefrontal mechanisms may be necessary for establishing effective retrieval strategies, monitoring the quality of retrieved information, and inhibiting irrelevant information. More generally, the prefrontal cortex may act as a central executive that allows for strategic control of long-term memory systems as well as control of modality-specific working memory mechanisms that temporarily hold and manipulate information.

REFERENCES