Chapter

11

Memory

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Human memory consists of several functional systems that collectively support the acquisition, retention, and subsequent retrieval of information. Much of what is known about different memory processes has been gleaned from experiments in non-human primates and other mammals, which allow for direct manipulation of experimental conditions but provide limited information about the human condition. Complementing animal lesion experimental data are individual case studies in a few human subjects uniquely affected with specific lesions that isolate different memory systems. Data generated from these select individuals have widely influenced current theories of memory function by yielding inferences regarding component processes and anatomical substrates based on brain–behavioral correlation. More recently, high-resolution structural and functional imaging methods have greatly facilitated the investigation of structure–function relationships associated with different human memory functions. In particular, functional magnetic resonance imaging (fMRI) allows for assaying neural circuitry in real-time during the performance of various memory tasks.

Memory systems are classified according to the temporal duration (short- vs. long-term memory) or the qualitative nature of the information being retained (Figure 11.1). Short-term memory (STM) generally refers to the retention of information over brief periods of time, on the order of seconds. Working memory (WM) is a form of STM that entails a temporary storage buffer for information that undergoes further processing; long-term memory (LTM) involves the acquisition and retention of information over longer intervals of time. Long-term memory can be further subdivided into declarative memory, which
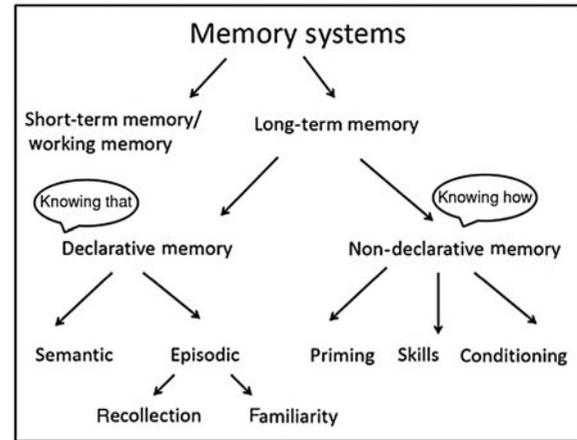

Figure 11.1. A framework for understanding memory and its subtypes.

refers to the acquisition and retention of knowledge, and non-declarative memory, reflecting experience-induced changes in performance.

In a clinical context, the temporal aspects of learning and memory are parsed into immediate recall (processing and recitation over a period of seconds), recent memory (anterograde learning over a period of minutes), and remote memory (retrograde recall of previously learned information). These terms reflect stages of information processing (encoding, storage, retrieval) that form the basis of standard clinical tests of verbal episodic memory (e.g., word-list or paragraph recall).

This chapter will review the clinical context and describe the functional–anatomic architecture of multiple memory systems including WM, declarative memory (i.e., semantic memory and episodic memory), and non-declarative memory (i.e., implicit

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memory and procedural memory). The account will be based on neuropsychological and functional neuroimaging studies of normal individuals and clinical populations.

Clinical overview

The anatomical substrates of memory include distributed networks of cortical and subcortical nuclei interconnected by white matter projection pathways. For example, the Papez circuit – comprising the entorhinal complex, hippocampal formation, fornix, mammillary bodies, and anterior/dorsomedial thalamus, and the cingulate gyrus – contributes to learning new information; lesions affecting any of these structures may interfere with this process, resulting in a learning or storage deficit [1]. Although susceptible to injury from a variety of insults, these structures are particularly susceptible to the effects of hypoxic-ischemic, hypoglycemic, or other metabolic injury (i.e., CA1 region of the hippocampus), increased glucose metabolism in the setting of thiamine deficiency (i.e., mammillary bodies and thalamus), trauma (i.e., hippocampus and fornix), and Alzheimer's disease (AD) (i.e., entorhinal complex–hippocampal formation). By contrast, injury to frontal–subcortical systems is more often associated with difficulty retrieving recently learned information (producing a retrieval deficit). Accordingly, lesions associated with traumatic brain injury, cerebrovascular disease, multiple sclerosis, HIV/AIDS, and other conditions may have a deleterious effect on frontal-subcortical circuits and are common causes of impaired memory retrieval. Degenerative conditions such as Parkinson's disease (PD) and Huntington's disease (HD) that affect basal ganglia and cerebellar structures involved in perceptual-motor processing may cause impairments in WM and procedural memory [2]. From a therapeutic perspective, research on memory functions has focused on remediating "core" cognitive deficits (i.e., short-term episodic memory deficits) in the setting of AD, and WM deficits in the context of attention-deficit disorder (ADD) and schizophrenia.

Memory impairment is the most common reason for seeking a cognitive evaluation, and this problem has multiple possible causes. In most cases, memory impairments are comorbid with other cognitive and neurobehavioral problems. Disorders such as herpes encephalitis, which has a predilection for limbic and paralimbic cortical regions, may cause an amnestic syndrome associated with other neurobehavioral features, such as personality change and seizures. Alcohol amnestic disorder (also known as Korsakoff's syndrome or Korsakoff's psychosis), transient global amnesia (TGA), and amnestic mild cognitive impairment (MCI) are the most common causes of isolated impairment of declarative memory. Although well known to be associated with Korsakoff's syndrome, an amnestic syndrome in which a tendency to confabulate features prominently also may develop after rupture of an anterior cerebral artery aneurysm. Secondary memory impairments may develop as complications of electroconvulsive therapy (ECT), epileptic seizures (i.e., complex partial or generalized seizures), or severe alcohol intoxication ("alcoholic blackouts"). A variety of nutritional, metabolic, endocrine, and toxic conditions may impair memory function directly or indirectly via compromise in attentional systems, as with an acute confusional state or delirium.

Multiple memory systems

Memory is not a unitary function, but instead denotes a large and diverse set of psychological processes and neural systems involved in learning and retrieving information. These processes include, among others, WM, declarative (episodic, semantic) memory, and non-declarative (implicit, procedural) memory, each of which will be considered in the following sections of this chapter.

Working memory

Working memory refers to the retention of information over brief intervals of time, typically on the order of seconds. It involves the temporary online storage and manipulation of information that can be used for immediate behavior, without being directly available to the senses. It is different from the notion of STM in that it is not merely a relaying stage prior to the storage of information in LTM. Rather, WM encompasses an array of cognitive processes. The amount of information WM can handle is both limited in time (approximately 20 seconds) and in capacity (approximately four to nine items), and is somewhat flexible. By actively rehearsing an informational item, one can keep information in WM for extended periods of time. Similarly, by grouping different items into meaningful chunks of information, WM capacity can increase substantially [3]. The limited capacity of WM allows cognitive scientists to study its nature using a dual-task

methodology. This research strategy is based on the assumption that if two activities are conducted in tandem and neither is impaired, then the processes do not depend on the same system. However, if performance on one task decreases as a function of being carried out along with the other task, then both tasks depend upon the same mnemonic system.

This methodology has been widely used by Alan Baddeley in shaping his WM model [4]. The model comprises four components: three material-specific slave systems and one central executive. One slave system is called the "phonological loop." It mediates the temporal storage and rehearsal of phonemes and sounds. As such, it is essential for language production and comprehension, as well as for the temporary storage of numeric and other symbolic representations. Experimental studies have shown that rehearsal and retrieval of information processed by the phonological loop is sensitive to phono-articulatory characteristics. It has been suggested, for instance, that the phonological loop stores information in a phonetic format, as evidenced by the phonological similarity effect in which recall is poorer for sequences of phonologically similar items [5]. Similarly, it has been suggested that phonological rehearsal involves high-level activation of speech-motor planning processes [6]. This claim finds support in the word length effect, which states that serial recall accuracy is correlated with length of phonological articulation – the longer and more complex the word, the longer it takes to rehearse.

Neuroimaging and neuropsychological studies support dissociation between phonological storage and rehearsal [7–9]. On the one hand, patients with damage to the left supramarginal gyrus of the inferior parietal cortex exhibit poor repetition, produce phonemic paraphasias, and have reduced auditory verbal span, deficits indicative of an impaired phonological store [10, 11]. On the other hand, patients with damage to the left inferior frontal gyrus display output deficits characterized by diminished phrase length and poor articulation, findings indicative of impaired articulatory rehearsal [11, 12]. Importantly, functional neuroimaging studies have shown that storage and maintenance of information involves interactions between posterior buffer regions and anterior rehearsal mechanisms. For example, verbal WM appears to be mediated by the left posterior parietal cortex, which subserves the phonological store, as well as Broca's area, the left premotor area,

and the left supplementary area, which are involved in articulatory rehearsal [13].

Another slave system is the visuospatial sketchpad, which stores and manipulates visual and spatial information. The visuospatial sketchpad is independent of the phonological loop, as it is associated with activity in the right – and not the left – cerebral hemisphere [14]. Additionally, it is selectively disrupted by concurrent activities that do not influence the phonological loop [15]. It is also thought to involve two different components: a visual store that preserves perceptual features of objects, and a spatial or sequential component that may serve a rehearsal function.

Neuropsychological findings offer strong support for this dissociation. Patients with occipital and temporal damage exhibit impaired visual storage, but preserved spatial WM [16]. In contrast, patients with parietal deficits show impaired spatial storage, but preserved visual WM [17, 18]. Recent research has also revealed that eye-movements play a key role in the maintenance of spatial, but not object, representations in the visuospatial sketchpad [19].

The final slave system, the episodic buffer, is the most recent addition to the model [20]. The function of this buffer is to represent and integrate inputs from all subcomponents of WM, as well as LTM, in a multimodal neural code. As such, it is thought to process multidimensional information that will later be consolidated or reconsolidated in episodic memory. Moreover, the episodic buffer is thought to link semantic information from the visuospatial sketchpad and the phonological loop in order to integrate this information into complex episodic representations via modulation by the central executive. The observation that amnestic patients can produce coherent episodic narratives despite profound deficits in LTM supports the postulated role of the episodic buffer. Although the precise neural correlates of this episodic buffer remain unspecified, preliminary fMRI evidence suggests that the right frontal lobe may play a key role [21].

Each of the aforementioned slave systems depends on a central executive system. This system, which is also limited in capacity, plays a fundamental role in complex memory span tasks (e.g., random digit generation) and it is closely linked to attentional control. Indeed, Baddeley [22] suggested that the central executive may in fact correspond to Shallice's [23] supervisory attentional system. It is thought to regulate the flow of information with WM, and the retrieval of material from more permanent LTM into WM.

In addition, the central executive permits attentional shifts between tasks as well as selective attention and inhibition.

Neuropsychological evidence suggests that there are two main types of dysexecutive syndrome, each reflecting dysfunction in the central executive system. One type involves marked perseveration, indicating decreased ability to disengage and shift attention, whereas the other is characterized by excessive distractibility, which reflects impairments in attentional inhibition. It has been observed that individuals with AD and frontotemporal dementias are impaired when performing concurrent multiple tasks, indicating that the frontal and prefrontal cortices may be selectively involved in the functioning of the executive system [24]. Furthermore, neuroimaging studies indicate that executive control processes are mediated by the cingulate and dorsolateral prefrontal cortices [25, 26].

Finally, it is worth noting that despite the influence of Baddeley's WM model, other models have been suggested. Of note is Nelson Cowan's [27] model, which unlike Baddeley's model, suggests that WM and LTM process the same types of memory representations. According to Cowan's model, there are not different kinds of systems operating upon different kinds of WM representations, but rather a unique executive system activating and deactivating memory representations via attentional modulation. Further research is needed to assess the relative virtues of these different models.

Declarative memory

Declarative memory encompasses the acquisition, long-term retention, and retrieval of events, facts, and concepts [28]. Such knowledge can be retrieved at will and used in a variety of contexts. Declarative memory can be subdivided depending on whether memories are concerned with personally relevant events (i.e., episodic memory) or impersonal information (i.e., semantic memory).

Episodic memory

Episodic memory enables individuals to recollect conscious experiences from their personal past (e.g., remembering what one had for breakfast this morning). According to Tulving [29], episodic memories are characterized by a sense of subjective awareness of having experienced the remembered events in the past.

To tap into this particular feeling or "recollective experience," Tulving developed the so-called remember/know paradigm. In this paradigm, participants are first presented with stimulus material and then asked to retrieve this information on a memory test. During recall, participants are asked whether they remember the studied event – that is, whether they can picture it in their minds with some detail – or, instead, if they only know that they have studied it (i.e., a sense of knowing something without being able to conjure up additional informational details).

This widely implemented paradigm has produced robust results, suggesting two different mnemonic processes: recollection and familiarity. As later suggested by Tulving [30], the hallmark of recollection is a sense of autonoetic (self-awareness) consciousness accompanying the recollective experience; it pertains, therefore, to episodic memory. On the other hand, the absence of autonoetic consciousness during familiarity evidences a different sort of processing, this time related to semantic memory. Although the nature and exact relation between recollection and familiarity is a matter of debate [31] convergent evidence suggests that episodic memory is a distinct memory system.

A pervasive deficit in episodic memory is dramatically exemplified in patients with anterograde amnesia, who are unable to acquire and retrieve any events or episodes from their personal life that occurred since the onset of their amnesia. This phenomenon was first documented in patient H.M., a man who, in 1953, underwent surgery for treatment of refractory seizures [32]. The surgery involved bilateral resection of the medial temporal region, which reportedly included removal of the amygdala, anterior two-thirds of the hippocampus, and hippocampal gyrus. Although the surgery was successful in substantially reducing H.M.'s seizures, the procedure produced a pervasive impairment of memory that was termed "global amnesia" [33]. From the time of his surgery at the age of 27 until his death in 2008, H.M. was unable to consciously learn and remember new episodic information.

Patients with global amnesia also manifest retrograde amnesia (i.e., the loss of memory for experienced events that occurred prior to brain injury onset). Frequently, remote memories are better preserved than memories for events that occurred shortly before brain injury. This effect, which was described over a century ago by Théodule Ribot [34] and referred subsequently to as Ribot's law, is only now coming to be understood,

as cognitive neuroscientists investigate how the hippocampus and surrounding medial-temporal structures contribute to the enduring storage of episodic memories.

Although there is general agreement that the hippocampus is critical for memory consolidation (i.e., the permanent laying down) of information, memory theorists disagree as to the role the hippocampus plays in the storage of consolidated memories. The traditional view suggests that the medial temporal lobes are not the ultimate repositories for new memories [35, 36]. Rather, storage of new memories requires interaction between medial-temporal and neocortical areas. The hippocampus receives input from distributed neocortical sites about an event to be remembered and forms a compressed representation that binds together the information from different sites that form a complete representation of that event. Partial reinstatement of the activation pattern associated with that event leads to a spreading of activation, whereby the initial pattern of neocortical activation is regenerated. Whenever a neocortical pattern is reinstated, the functional connections between constituent sites are reinforced. Over time, permanent cortico-cortical connections are established, allowing a memory to be retrieved without mediation from the limbic system. As a result, information that is not fully consolidated is vulnerable to partial or complete loss in the setting of hippocampal damage, whereas fully consolidated (i.e., older, representationally stable) memories are able still to be retrieved successfully.

More recently, alternative views have been proposed in which the hippocampus plays a more permanent role in the retrieval of episodic memories. One such theory, known as the Multiple Trace Theory [37], suggests that recollection of episodic memories always depends on the hippocampus, and that every time one recollects an episodic memory, a new memory trace is created. Thus, episodic memories that are more frequently remembered have been coded in multiple traces, rendering them less vulnerable to damage. Other views suggest that the hippocampus is always required for recollection, but not for familiarity [38, 39], insofar as it permits the recombination of episodic components into a single memory event [40]. Finally, some views suggest that the hippocampus stores allocentric (i.e., non-self-centered) representations of spatial context, which allow humans and other mammals not only to navigate their immediate surroundings, but also to mentally access the spatio-temporal content of their memories. Further research is needed to fully understand the specific role of the hippocampus and the medial temporal lobes in retrieval.

Neuroimaging studies provide additional evidence for the role of the medial temporal lobes in episodic memory. Activation of the medial temporal region is observed during both initial registration of novel events and also during retrieval of recently acquired information [41, 42]. Medial temporal lobe activity is greater during the encoding of experiences that are later remembered versus those that are later forgotten [43, 44].

Episodic memory also depends on frontal lobe function. Although patients with frontal lobe lesions may demonstrate normal performance on tasks of recognition memory, prose recall, and some cued recall tasks, they typically show impairments on free recall, memory for temporal order, and source memory tasks [45]. These latter tasks depend on elaboration of information at encoding, as well as monitoring and decision processes at retrieval – strategic processes proposed to be mediated by frontal regions. On recognition tests, some patients with frontal lesions (primarily in the right hemisphere) make an unusually high number of errors in which items are designated as "old" when they in fact are "new" (i.e., false alarms) [46, 47]. Additionally, Levine and collaborators [48] reported the case of M.L., who after suffering closed head trauma, experienced a severe episodic retrograde amnesia: he was unable to remember any autobiographical experiences prior to the accident. Interestingly, M.L. did not experience anterograde amnesia, as he was still able to encode and further recall events occurring after the accident. M.L.'s pathology was restricted to the right ventral frontal lobe, including the uncinate fasciculus, while his hippocampus was intact. Taken together, these cases indicate that while the hippocampus is essential for encoding episodic information, the frontal lobes are essential for episodic recollection.

Finally, the most recent conceptual development in our understanding of episodic memory is the relationship between remembering the past and imagining the future. When studying patient K.C. – an individual whose case offers the clearest known example of a dissociation between episodic memory and semantic memory [49] – researchers noted his inability to remember the past in concert with his inability to envision himself in the future. The capacity to think about

one's future is related to the capacity to remember previous episodes from one's life [50]; more specifically, these capacities share the same neural underpinnings [51–54] and are phenomenologically [55] and ontogenetically related [56].

Semantic memory

Semantic knowledge encompasses a wide range of information, including facts about the world, the meanings of words and concepts, and the names attached to objects and people. Unlike episodic memories, semantic memories can be retrieved without associated information regarding the context in which they were acquired.

By virtue of its diverse nature, not all forms of semantic knowledge share the same properties. Some forms of knowledge can be acquired after a single exposure (e.g., knowledge that Lisbon is the capital of Portugal), whereas other forms may be gradually acquired across multiple repetitions (e.g., understanding the concept "website"). Additionally, semantic information, when first encountered, may vary in the extent to which it is truly novel. For instance, semantic learning may involve establishing new associations between pre-existing representations in memory (e.g., learning that William Shakespeare wrote *Romeo and Juliet*) or acquiring a new label for information already represented in memory (e.g., foreign-language learning). Finally, a new label and a novel set of properties may be linked to each other (e.g., learning the meaning of the word "microbrew").

Neuropsychological studies of semantic memory have focused on brain lesions that selectively impair different stages of information processing (i.e., acquisition, storage, or retrieval) as well as the organization of knowledge. Evidence for the neural structures subserving the acquisition of new semantic knowledge has come primarily from studying patients with amnesia. Patients with extensive medial temporal lesions, such as amnesic H.M., are unable to acquire the meanings of words that entered the language after the onset of their amnesia [57, 58]. Some findings suggest that the integrity of structures surrounding the hippocampus (subhippocampal cortices) may be critical for new semantic learning. Vargha-Khadem and collaborators [59] reported three young amnestic individuals who sustained severe bilateral hippocampal atrophy as a result of anoxia. Importantly, their deficit appeared to be confined to episodic memory, as they were unable to remember or encode any specific events of their lives,

while their capacity to remember and learn new facts was preserved. Inspection of available neuroanatomic data revealed that in all three children, damage was limited to the hippocampus proper with sparing of subhippocampal cortices. These cases suggest that while the hippocampus is necessary for episodic memory, subhippocampal cortices may mediate semantic memory. Consistent with these findings, an adult patient with hippocampal and subhippocampal damage demonstrated profoundly impaired episodic and semantic learning, whereas another adult patient with only hippocampal damage had disproportionately preserved semantic learning [60].

Whereas subhippocampal cortices appear critical for acquiring new semantic information, these areas are not implicated in information storage. Studies of patients with semantic dementia or focal temporal lobe lesions suggest that semantic knowledge is stored/represented in the lateral temporal lobes in a distributed network of information [61, 62].

Memory retrieval requires interaction between retrieval cues and stored representations so as to trigger cortical storage sites to provide memory output. This retrieval process is thought to be mediated by inferolateral frontal and temporopolar regions, as patients with lesions in these areas, especially in the left hemisphere, have significant difficulty retrieving old semantic memories [63]. Neuroimaging studies also have shown activation in these areas when normal subjects make semantic judgments about objects or words [64].

Insight into the organization of semantic memory has come from investigating patients with circumscribed lesions who demonstrate category-specific knowledge deficits. An especially striking dissociation has been observed between knowledge of living and non-living things. Some patients have impaired knowledge of living things (e.g., animals and vegetables), but preserved knowledge of non-living things (e.g., tools and furniture), whereas other patients show the reverse pattern [65, 66]. One interpretation of category-specific deficits is that semantic memory is represented in the brain according to taxonomic categories. Another interpretation is that categories differ in their reliance on knowledge from different sensorimotor modalities, with living things known predominately by their visual attributes and non-living things by their function. Accordingly, category-specific knowledge deficits for living and non-living things may reflect impairments in the

representation of visual and functional knowledge, respectively.

Consistent with the neuropsychological literature, pioneering neuroimaging studies showed differential activations for category-specific stimuli. Using positron emission tomography (PET) scans, Martin and collaborators [67] found greater activation in left medial occipital cortex during naming pictures of animals relative to pictures of tools. In contrast, naming pictures of tools revealed greater activation in left premotor and middle temporal cortices. Additionally, several neuroimaging studies showed activation in left prefrontal cortices during semantic retrieval [68].

Perhaps the stronger piece of evidence supporting the observation that left-lateralized damage to the anterior temporal cortex affects semantic rather than episodic memory comes from patients suffering from semantic dementia. One of the best-documented cases of semantic dementia is patient A.M. [69]. Upon examination, A.M. showed severe difficulty remembering the names of things (anomia), even though his speech and prosody remained largely intact. Further testing revealed intact non-verbal episodic retrieval, evidenced by normal performance during tasks such as copying the Rey complex figure. More recently, Davies and collaborators [70], using post-mortem data from a group of seven individuals with semantic dementia cases, discovered that, relative to controls, semantic dementia was associated with anterior temporal atrophy, including parts of the perirhinal cortex, and preservation of adjacent areas in the temporal lobe. The extent to which other brain areas are implicated in semantic memory, as well as the nature of semantic representations in memory, remains an area of active scientific research.

Non-declarative memory

Non-declarative memory refers to a variety of forms of memory in which learning is expressed as enhanced performance [71]. In this chapter, we focus on two forms of non-declarative memory: implicit memory and procedural memory.

Implicit memory

Implicit memory describes a type of non-declarative memory in which previous experiences aid task performance without any requirement for conscious awareness of those previous experiences [72]. One well-studied form of implicit memory is repetition priming (referred to as "priming" hereafter). A typical priming task is comprised of study and test phases. During the study phase, participants are exposed to a series of words, pictures, or objects. For example, they might see a word list that contains the word "turnip." During the test phase, participants perform a seemingly unrelated task. For example, they might have to identify briefly flashed words or generate as many words as possible when cued with the semantic category "vegetable." Priming is measured as the facilitation in task performance induced by recent exposure to task stimuli (e.g., enhanced accuracy in identifying or generating the word "turnip"), as compared with a baseline condition in which that word had not appeared on the prior study list.

Studies in normal participants have identified two types of priming: perceptual priming, which requires analysis of the perceptual attributes of a stimulus (e.g., identification of perceptually degraded stimuli), and conceptual priming, which requires analysis of the meaning of a stimulus (e.g., category exemplar generation) [73]. Importantly, these two types of priming are differentially affected by experimental manipulations that vary the amount of overlap between study and test phases. A change in the perceptual format between study and test reduces perceptual priming, but has no impact on conceptual priming. Alternatively, enhanced conceptual priming occurs with elaborate processing of stimuli at study versus when only shallow processing occurs; this processing manipulation has no effect on perceptual priming.

Neuropsychological investigations indicate that globally amnesic patients show intact performance on perceptual and conceptual priming tasks [74]. This finding suggests that the mnemonic operations involved in priming are not dependent on the medial temporal and diencephalic structures implicated in global amnesia. Like globally amnesic patients, AD patients have pathologic changes in limbic structures and show impairments on declarative memory tasks. Unlike amnesic patients, however, those with AD also have extensive neocortical pathology, particularly in frontal, temporal, and parietal association areas [75], and show impaired conceptual priming despite preserved perceptual priming [76, 77]. This pattern of impaired and preserved priming in AD suggests that conceptual priming processes may be localized to frontal, temporal, and parietal association areas that are compromised in AD. In contrast, perceptual priming processes may be localized to early

modality-specific cortices that are relatively spared in AD. Further neuropsychological evidence that perceptual priming is mediated by modality-specific cortices comes from patients with focal occipital lobe lesions who show impaired priming on visual perceptual tasks and preserved priming on conceptual tasks [78, 79]. Taken together, these findings lend strong support to the notion that perceptual and conceptual priming are mediated by separable neural substrates.

Neuroimaging studies aimed at localizing priming processes are generally consistent with findings from clinical studies [80]. Visual perceptual priming is mediated by visual association areas, whereas conceptual priming is mediated by more anterior cortices (e.g., superior temporal and anterior frontal regions). Furthermore, these studies have demonstrated that the facilitation resulting from repeated processing of a stimulus is associated with decreased neural activation (also called response suppression) for repeated stimuli relative to new stimuli. Depending on the technique, the reduction in hemodynamic response can be measured as decreased regional cerebral blood flow (using PET) or as decreased blood oxygen-level dependent (BOLD) signal (using fMRI). Using event-related fMRI, Henson, Shallice and Dolan [81] presented a series of familiar faces and familiar symbols while subjects were instructed to search for a target. Simply viewing repeated faces or symbols was associated with decreased neural activation in the fusiform gyrus. Such decreases in neural activity have been interpreted to map onto the behavioral priming effect, as the facilitated, more efficient processing of previously perceived stimuli (see [82] for a thoughtful discussion of this issue).

According to one model [83], such decreased activation reflects a neural tuning, or sharpening mechanism, in which only the neurons that respond best to the stimulus are recruited for reprocessing that stimulus at a later time (but see [82, 84] for important caveats with regard to this model). Neural priming is typically evident in areas of stimulus- or concept-specific processing, such as extrastriate cortex of the occipital lobe (for visually perceived stimuli), fusiform cortex (for object or face stimuli), primary auditory cortex in lateral temporal lobe (for aurally perceived stimuli), or inferior frontal gyrus (for priming of semantic information).

More recently, Schacter and colleagues [85] reviewed numerous studies reporting reductions in cortical activity during priming. Their review yielded several observations. First, prefrontal regions demonstrate sensitivity to both conceptual- and stimulus-decision mapping components of repetition priming. Robust correlations have been observed between the magnitude of behavioral priming and neural priming in this region, and trancranial magnetic stimulation (TMS) applied to the left prefrontal cortex (PFC) during semantic classification tasks disrupts subsequent behavioral priming. Second, regions in the lateral temporal cortex demonstrate sensitivity to conceptual components of repetition priming and, similar to prefrontal regions, respond amodally. Third, perceptual cortices demonstrate sensitivity to perceptual components of priming and tend not to be correlated with behavior during tasks that encourage conceptual or semantic priming. Neural priming in these regions demonstrates a gradient of stimulus specificity such that the degree of stimulus-specific priming decreases as one proceeds from early (posterior) to late (anterior) regions with the perceptual system, and there is a laterality effect (i.e., less specific in the left than right hemisphere) across later visual regions.

Procedural memory

Procedural memory is involved in the acquisition of skills and habits, results from repeated practice, and is relatively impervious to the effects of decay or interference. Research studies investigating the acquisition of new perceptual-motor skills have employed simple tasks, such as mirror tracing or rotary pursuit. During mirror tracing, a participant uses a metal stylus to trace a geometric pattern seen in a mirror, while the geometric pattern and the individual's hand are obscured from view by a board. Learning is measured by the reduction in time to complete tracing of the pattern, as well as the number of errors committed. During rotary pursuit, a participant is given a metal stylus that must be kept in contact with a revolving disk. Learning occurs as the individual becomes more proficient at matching his or her motor movement with the movement of the disk.

Early studies of patient H.M. were among the first to establish that globally amnesic patients could acquire and retain new motor skills [33, 86]. Such findings are especially significant given that these patients are frequently unaware of having been previously exposed to the tasks. These results suggest that procedural memory is mediated by neural structures outside the medial temporal-diencephalic region.

In contrast to amnesic patients, other neurological populations, such as PD and HD patients, have poor rotary pursuit learning [87]. Based on these data, it appears that the basal ganglia, which are compromised by these diseases, play a critical role in motor skill learning. However, basal ganglia lesions do not impair all motor skill tasks to the same extent; for example, Gabrieli and colleagues observed that HD patients demonstrate normal mirror tracing despite impaired rotary pursuit learning [88]. In contrast, patients with cerebellar lesions show impaired mirror tracing [89]. These observations suggest that the basal ganglia and cerebellum both contribute to motor skill learning but do so differentially: the basal ganglia are critical for sequence learning whereas the cerebellum is involved in error correction [88].

The perceptual skill that has been studied most extensively in neurological patients is learning to read text that has been geometrically transformed (such as reading mirror-reversed words). Current interest in perceptual skill learning was driven by the classic study of Cohen and Squire [90] in which they examined the performance of amnesic patients on the mirror reading task. The results of the study showed that the amnesic patients were able to learn to read mirror-reversed text as well as age-matched control participants, despite having poor declarative memory for the practice episodes and stimuli. Subsequent studies have replicated these findings in other groups of amnesic patients [91, 92].

Evidence for the role of the basal ganglia in perceptual skill learning comes from patients with HD, who show a mild impairment in mirror reading, despite good declarative memory for the words read [91]. Studies of mirror reading in patients with PD have been mixed, however, with some studies reporting impaired learning [93–95] and other studies reporting intact learning [96, 97].

Perceptual learning studies in healthy adults have used psychophysical tasks such as contrast detection, orientation, and visual search [98, 99]. This research suggests that perceptual learning proceeds in two stages: an initial learning stage, characterized by unskilled and effortful performance, that reflects establishment of task-specific processing routines; and a subsequent stage, ultimately leading to skilled performance, reflecting modification of representations within the processing system [100].

Accordingly, functional imaging studies have demonstrated different neural contributions in the early versus later stages of skill learning. For instance, a study of mirror-reversed reading in normal subjects demonstrated that skill acquisition was accompanied by decreasing activation in regions including both occipital and right superior parietal cortices during initial learning, and increasing activation in regions including the left inferior temporal cortex later on [101]. On the basis of these results, it was proposed that learning to read mirror-reversed text may reflect a transition from right hemisphere visuospatial processing of mirror-reversed stimuli to left hemisphere object recognition areas involved in establishing new representations of mirror-reversed letters [101, 102]. Interestingly, in a follow-up study, Poldrack and Gabrieli [103] found that the caudate was active during initial mirror-reading and showed a significant learning-related increase in activation, consistent with the reported impairment of HD and PD patients in learning the mirror-reading task.

In an analogous manner, studies investigating the acquisition of new motor skills have revealed that prefrontal and cerebellar regions are primarily activated early in the course of learning [104, 105]. As task proficiency increases, this activation gives way to a slowly evolving, long-term, experience-dependent reorganization of primary motor cortex [106]. More recent studies have further delineated the roles of prefrontal, cerebellar, and motor cortices during motor skill learning, as well as the parameters under which new motor skill learning occurs. For example, using fMRI and a motor sequence task, Doyon and colleagues [107] found evidence for an experience-induced shift from the cerebellar cortex to the dentate nucleus during early learning, and from cerebellar-cortical to striatal-cortical networks with extended practice; these findings suggest that intrinsic modulation within the cerebellum, together with activation of motor-related cortical activations, serves to establish a procedurally acquired sequence of movements. More recently, Doyon and colleagues [108] investigated the contribution of sleep to consolidation of two motor skills: finger tapping sequence learning (FTSL) and visuomotor adaptation (VMA). They demonstrated that the consolidation processes involved in the FTSL task benefited from sleep (even a short nap) while the simple passage of time was as effective as sleep time for the consolidation of VMA to occur. Such findings point to important task differences in the study of motor skill learning. Finally, Rozanov, Keren and Karni [109] examined the specificity of memory

for a highly trained finger movement sequence. Their results demonstrated that the gains attained in the performance of a well-trained sequence of motor movements can be expressed only when the order of the movements is exactly as practiced. These results may have important implications for the transfer of new motor skills in patient populations, particularly in neurorehabilitation efforts directed at improving motor functions impaired by injury or disease.

Conclusion

Multiple human memory systems subserve the retention of knowledge, skills, experience, and emotions over a time frame that spans seconds to decades. Neural pathways that encode information within these overlapping systems are being elucidated with structural and functional brain imaging techniques and sophisticated cognitive test paradigms. Such work is enriching our understanding of component memory processes and has great potential for informing clinical diagnostic and therapeutic efforts. Translating research advancements in the cognitive neuroscience of memory into practical clinical assessments and interventions will be greatly facilitated by increased collaboration among basic scientists, clinical investigators, and clinicians.

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