

MEMORY: SYSTEMS, ABILITIES, DEFICITS, DISORDERS

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Memory function is critical to daily life, and includes a variety of specific abilities that, at their core, enable information to be stored (at least briefly) for future use. Most memory abilities are evolutionarily primitive but have been elaborated at least to some degree in humans, although episodic memory is thought to be evolutionarily recent and its existence in many animal species is debated. Four major forms of memory are episodic, semantic, working, and procedural memory (Budson and Price, 2005, 2007). The focus of this discussion is on episodic memory, but the other forms of memory will be briefly reviewed since the clinical evaluation (and experimental probing) of a specific memory ability usually requires the interpretation of function in these other domains.

It is important to recognize that most of the observations and hypotheses described below owe at least some credit to one of the world's most famous neurologic patients, H.M., who died on December 4, 2008, at the age of 82. Studies that were initiated in work with him by Professors Brenda Milner, Suzanne Corkin, and many others led to the development of methods for measuring memory dysfunction and to seminal concepts regarding the brain's multiple memory systems. Readers interested in additional information are referred to the New York Times obituary and to the forthcoming book by Dr. Sue Corkin.

Clinical aspects of memory abilities

Procedural memory

Procedural memory is the ability to produce a series of movements or actions that have previously been learned, such as swinging a golf club, riding a bicycle, or driving a car. This form of memory is usually classified as "implicit" or "non-declarative" because it is difficult or impossible to describe or even understand exactly what is being done to achieve the goal (i.e., it is below the level of conscious awareness).

Procedural memory systems are thought to be localized in cortical (supplementary motor area and rostral superior parietal lobule) and subcortical (basal ganglia, cerebellar, and probably other deep structures) brain regions. Procedural memory is impaired in diseases affecting these systems, such as extrapyramidal disorders (e.g., Parkinson's disease), cortical disorders of the peri-Rolandic regions (e.g., corticobasal degeneration), and cerebellar diseases. Focal lesions including strokes and tumors, as well as metabolic disorders affecting specific components of these systems (e.g., Wilson's disease), can compromise procedural memory.

Symptoms of procedural memory loss usually include complaints of the loss of specific skills in the absence of weakness or fundamental coordination or other sensorimotor abnormalities. Procedural memory is not commonly well tested clinically, in part because patients' premorbid skills vary widely in many motor abilities. Approaches to the testing of limb praxis are generally well-suited for the interrogation of procedural memory. Testing of the

acquisition of new motor sequences can also be used, but there is a paucity of formal testing methods for this purpose.

Semantic memory

Semantic memory is memory for factual knowledge that has been learned but for which specific “time and place” source information for the original experience with the information is typically not known. Encyclopedic knowledge of information such as the features of objects (e.g., apples are usually red), categories (e.g., oranges and bananas are both types of fruit), historical events, and similar types of information are considered to be stored in semantic memory systems of the brain.

Semantic memory systems are generally thought to be localized in distributed regions in temporal and parietal cortices. For the most part, semantic memory is relatively resilient to neurologic disorders, but can be compromised by some disorders with predominant effects on temporal and parietal cortices, including neurodegenerative diseases (particularly the temporal variants of frontotemporal dementia, such as semantic dementia, but also Alzheimer’s disease), and cerebrovascular and other focal lesions affecting ventrolateral temporal lobes, as well as some infectious or inflammatory conditions, particularly herpes encephalitis.

Clinically, disorders of semantic memory often cause changes in speech and comprehension of language, with difficulty finding specific words such as the use of so-called superordinate words (e.g., bird instead of pigeon or owl). Fluent but vague speech is often present, but even when asked to point to pictures named by the examiner patients may have difficulty, indicating a “two-way” naming deficit consistent with a loss of semantic memory, rather than simply a naming problem. In order to identify a specific semantic memory deficit, detailed language testing is usually required.

Working memory

Working memory involves the very short-term maintenance of information in mind, and often the manipulation of that information for the purpose of achieving an immediate goal. The classic example is remembering a phone number while picking up and dialing a phone, but working memory is also important for comprehending long written or spoken sentences, performing calculations, and learning new information or a series of movements. Performing multiple simultaneous tasks also requires working memory.

Working memory systems are localized primarily in frontal and parietal cortices, but also involve basal ganglia as well (frontostriatal loops). Working memory is impaired in disorders affecting these systems, including cortical (e.g., Alzheimer’s disease, frontotemporal dementia) and subcortical (e.g., Parkinson’s disease) neurodegenerative diseases, as well as disorders of the white matter such as cerebrovascular disease, multiple sclerosis and other demyelinating diseases, and infectious/inflammatory diseases involving these systems. In addition, working memory depends heavily on an appropriate level of attention and arousal, and so can be prominently affected in psychiatric disorders as well as general medical disorders, in addition to medication affects. Specifically, there are important effects of acetylcholine, dopamine, and norepinephrine on working memory, so disorders or medications that modulate these systems can disrupt working memory abilities.

Symptoms of working memory loss include complaints about difficulties with concentration, distractibility, loss of “train of thought or conversation,” difficulty multi-tasking, or difficulty following the steps of a task. Working memory provides the basis for many aspects of executive function, and also for the learning of new information (encoding), and so deficits can impair new episodic or procedural learning. Working memory is commonly tested in the office using digit span or spatial span tasks, the spelling or recitation of sequences in forward and reverse order, performance of tasks involving alternating sequences (such as Trail Making), or N-back tasks.

Episodic memory

Episodic memory involves the ability to learn, store, and retrieve information about ongoing experience. This typically includes the time and place of an event, as well as information about the event itself. The ability to describe the details of a recent holiday gathering or office meeting that took place in the previous weeks or months, for example, depends heavily on intact episodic memory function.

Episodic memory systems are classically localized in the limbic system, including medial temporal lobe (hippocampal formation and entorhinal, perirhinal, and parahippocampal cortices), fornix, anterior and dorsomedial nuclei of the thalamus, mammillary bodies, and septal nuclei. There are also important contributions to learning and retrieval by the prefrontal cortex. Recently, regions of the parietal cortex have become the subject of intense investigation in relation to episodic memory (see below). Disorders of episodic memory include neurodegenerative diseases (particularly Alzheimer’s disease), forms of temporal lobe epilepsy (particularly mesial temporal sclerosis), toxic and nutritional abnormalities (Korsakoff’s syndrome), and infectious and immunologically mediated disorders with a predilection for medial temporal lobe and limbic systems (e.g., herpes encephalitis, limbic encephalitis), as well as cerebrovascular disease affecting these systems (particularly posterior cerebral artery and thalamic infarcts). There can also be transient abnormalities of episodic memory, including transient global amnesia, complex partial seizures, and similar syndromes.

Symptoms of episodic memory loss include the inability to recall recent events or conversations, often accompanied by repetitive asking of questions, misplacing of objects, and inability to recognize recently encountered people or places. Becoming lost or disoriented while driving can result from episodic memory loss, but can also be a result of other cognitive disorders. In the office, episodic memory is usually tested by teaching a patient a list of words or a short story and asking the patient to recite the information again in 5-20 minutes. Depending on the situation, episodic memory may be investigated more systematically using tasks that ensure the encoding of information (multiple repetitions of word lists followed by immediate recall tests), with the subsequent testing of free recall, cued recall, and recognition of the information (e.g., as implemented in the California Verbal Learning Test).

The cognitive neuroscience and functional neuroanatomy of episodic memory

Although a tremendous amount of knowledge about episodic memory has accrued from studies of animals, patients with brain disorders, and behavioral experiments, over the last 15-20 years, functional neuroimaging studies have greatly expanded our understanding of the brain systems that subserve normal human episodic memory abilities. Functional

neuroimaging/brain mapping techniques, coupled with increasingly sophisticated cognitive neuroscientific behavioral experimental approaches, have provided a major force for the evolution of thinking about the brain processes involved in and subserving episodic memory.

Professor Endel Tulving, the psychologist who coined the term “episodic memory,” writes about episodic memory as being arguably uniquely human and enabling “mental time travel.” He posits that there are at least three elements of the episodic memory system that are necessary for mental time travel, including A) the subjective sense of time, B) “autonoetic awareness,” or the sense that remembered events are from the past as distinct from present experience, and C) a sense of the self as the “time traveler” (Tulving, 2002).

Episodic memory is no longer thought to include “just the facts” of recent experience, as would be present in a recorded conversation. The content, or “what,” of episodic memory is what is usually tested in the clinic and often in the laboratory. It has become clear that additional information about the previous experience, or source, is important to episodic memory in the natural world, including “when” and “where.” Additional aspects of experience are also an integral part of the episodic memory trace, including emotional/affective state. Episodic memories are consolidated over time partly through a re-experiencing or re-telling of stories, usually as part of a social context, in a manner that can produce subtle or even prominent changes in the material remembered, often leading to the development of “false memories” which may or may not be consistently reproduced over time.

The sequence of steps that underpin episodic memory includes encoding, storage, and retrieval. Encoding processes involve the depth of encoding (“shallow” encoding employs perceptual attributes of stimuli while “deep” encoding engages thought about the meaning of stimuli), as well as encoding strategies (such as reorganizing or chunking information). Thus, it is clear that encoding (as well as retrieval) depends heavily on other cognitive functions, including semantic memory, working memory, executive control processes, and others.

The retrieval of information is commonly tested using free recall, various forms of cueing, or recognition procedures. Although responses to recognition testing were formerly viewed behaviorally in the simple terms of success or failure, investigations over the last decade have focused on the quality of experience during recognition, with the dual process model of recognition memory providing an important theme of many investigations. The dual process model proposes that successful recognition memory can be performed employing familiarity or recollection. Familiarity is marked simply by a sense of “knowing” that something has been encountered previously but not necessarily the capability to retrieve any specific details about the prior experience, as in a gut instinct that a person at the airport gate is someone encountered before. Recollection involves the ability to retrieve at least some specific details about “what,” “where,” and “when” of past experience, such as the knowledge that the person in the airport was at a conference on a related topic last year in Chicago. It is also important to recognize that a retrieval event can also be viewed as a re-experiencing or repeated encoding event.

The period of time between encoding and retrieval is thought to involve consolidation, a relatively ill-defined concept that has received little systematic investigation, at least in humans. A major reason for invoking a finite consolidation period is that, at some point after encoding, the ability to retrieve information becomes less dependent on hippocampal and

other medial temporal lobe structures, with the implication that the storage of information is ultimately performed by extra-hippocampal cortical brain systems.

An exciting and relatively recent avenue of study that may shed light on consolidative processes is the investigation of sleep and memory. Recent human data indicate various improvements in memory performance following a period of sleep, and animal data demonstrate a “replaying” of neurophysiologic firing patterns during sleep that were originally present while animals were performing tasks in the waking state.

Finally, the study of time and memory is gaining momentum. In particular, “prospective memory” is a new term for the imagining of the self in the future and the potential activities or actions that may take place (Schacter et al., 2008). Although the fundamental behavioral properties of prospective memory are still being worked out, it is thought that there are many similar characteristics to episodic memory of past events, including in some cases specific “what, when, and where” elements. Furthermore, it appears that patients with amnesia, Alzheimer’s disease, and other episodic memory disorders perform relatively poorly on prospective memory tasks, suggesting that both processes may be impaired under similar conditions. A great deal of work remains to deepen this line of inquiry, but some of the emerging concepts resonate with our experience with patients in the memory clinic, engendering some hope that investigation in this area may illuminate the basis for the repeated questioning of caregivers about future events in which many amnesic patients engage.

Functional neuroanatomy of episodic memory

A large number of animal and human experiments have continued to refine our thinking about the functional neuroanatomy of episodic memory systems in the brain. Although structures in the limbic system, as described in the first section above, are still considered important for episodic memory, several new themes have emerged particularly with respect to cortical circuits involved in episodic memory (Buckner, 2004) and the specific functional organization of the medial temporal lobe (Squire et al., 2004).

In the neocortex, it is becoming clear that regions of the prefrontal cortex, temporal cortex, and parietal cortex play important roles in episodic memory encoding and retrieval processes. Lateral prefrontal cortex appears to play an important role in semantic processing and elaboration of information during encoding, and in the use of strategies during both encoding and retrieval. One influential model suggests that there are left-lateralized processes engaged during encoding while right-lateralized processes are engaged during retrieval. The temporal neocortex is also important for aspects of semantic processing during encoding. Finally, several regions of the parietal cortex, particularly precuneus/retrosplenial cortex medially and inferior parietal lobule laterally, appear to play important roles in both encoding and retrieval, with some suggestions that precuneus may be involved in metamemory (“knowing that you know”) and inferior parietal lobule being involved in the explicit decision about whether information is old (“previously encountered”) or new, whether or not that decision is correct (Wagner et al., 2005).

The organization of processing streams within the medial temporal lobe appears to draw on separate cortical systems for processing visual information about objects vs. spatial

context, ultimately enabling the associative binding of that information into a coherent experience that can be retrieved in the future (Eichenbaum et al., 2007). A current hypothesis outlines the systems as follows. Visual information is processed in the occipital cortex and, in parallel, transmitted to occipitoparietal systems involved in interpreting the elements and organization of spatial information, along with occipitotemporal systems involved in perceiving and understanding the features of objects and ultimately integrating them with semantic and lexical information. The “where” system of the parietal cortex provides inputs to posterior parahippocampal cortex, which then provides afferents to medial entorhinal cortex. The “what” system of the temporal cortex provides inputs to perirhinal cortex, which then transmits information to lateral entorhinal cortex. Medial and lateral entorhinal cortices ultimately converge within the hippocampal formation on dentate gyrus and CA3, where it is thought that this information is processed in an associative fashion that later enables retrieval. Some data are beginning to suggest that one role of CA1, which also receives information from entorhinal cortices as well as from CA3, is to provide a “time stamp” for this information, thus providing one element of the poorly understood systems that capture the temporal sequence of experiences.

Finally, no contemporary discussion of episodic memory systems would be complete without a discussion of the “default mode” network (Buckner et al., 2008). A prominent line of functional neuroimaging research has identified a set of brain regions that are relatively more active during undirected epochs of time during experiments than during epochs involving the directed performance of a task, regardless of whether the task is primarily sensorimotor, cognitive, or affective. These brain regions include posterior cingulate/precuneus, lateral inferior parietal lobule, lateral and medial temporal, and medial prefrontal cortices. Many of these brain regions are implicated in one or another aspect of memory encoding or retrieval processes, as illustrated by memory task-related functional neuroimaging experiments. This observation has led to the hypothesis that one activity that may be prominently occurring during these “rest” epochs is thinking about the past or future, or “mental time travel,” which engages episodic memory systems of the brain. Questions related to these hypotheses are currently the subject of intense investigation.

Translating cognitive neuroscience of episodic memory into the clinic

Although knowledge of the cognitive processes and neural substrates of episodic memory have advanced substantially over the past several years, to date little of this knowledge has been systematically translated into clinical practice. In many busy neurology clinics, there may not be time for much more than the Mini Mental State Exam with its simple verbal encoding and free recall task. Yet with new billing codes for the interpretation of cognitive testing, it may be possible to make more sophisticated cognitive testing a routine part of clinical practice, at least in some settings. And with growing movements toward support for the interpretation of neuroradiologic studies by neurologists along with functional MRI billing codes, it may be possible for neurologists to spend more time actively engaged in probing the anatomy and function of specific brain memory systems in patients with memory disorders.

From a practical standpoint, it is critical to perform at least three activities in the assessment of patients presenting with memory symptoms (Knopman et al., 2001). A history focused on the types of memory complaints in daily life taken with an aim of grading the severity of difficulty in activities representing separate domains of memory is essential. This

history should be taken from both the patient and a knowledgeable informant. Informant (and sometimes patient) history can be taken with the assistance of a questionnaire that can be completed in advance or in the waiting room. If the symptom appears to be related to episodic memory dysfunction, focused testing should be performed of episodic memory. I typically employ a California Verbal Learning Test-type design with 6 to 10 words depending on the patient. Immediate free recall performance across a series of learning trials can be very informative with respect to attention, executive function, and the use of strategies. Delayed (typically 10 minutes) free recall, semantic category cued recall, and 3-choice recognition testing can be used to test retrieval. In some cases it can also be helpful to perform a similar procedure with pictures. Finally, an MRI scan including axial FLAIR, thin-slice T1 coronal, and susceptibility-weighted sequences is important to assess for the most common forms of pathology, including relatively specific atrophy patterns consistent with Alzheimer's disease and related disorders.

This three-pronged approach will enable common memory disorders to be identified and differentiated, and assist in the determination of whether a patient needs to be referred for neuropsychological testing or other additional procedures. Hopefully, in the future, through partnerships between neurologists, neuropsychologists, psychiatrists, radiologists, and neuroscientists interested in memory, we can expand our clinical armamentarium to include additional tools drawn from fundamental advances in the cognitive and imaging neuroscience of memory (Dickerson and Eichenbaum, 2010).

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