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Review

The brain basis for episodic memory: Insights from functional MRI, intracranial EEG, and patients with epilepsy

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Abstract

This article reviews the contributions that functional magnetic resonance imaging (fMRI), intracranial electroencephalography (iEEG), and patient studies have made to our current understanding of how memory functions arise from the brain. First, we briefly discuss the current classification of different memory systems and their neuroanatomical correlates, focusing on episodic memory and evidence from lesion studies. We then survey both fMRI and iEEG studies of memory function. For each modality, we discuss its physiological basis, as well as point out key studies that have led to new insights regarding memory. Advantages and disadvantages of each brain mapping modality are addressed. Wherever appropriate, we point out implications these studies have for the treatment of patients with epilepsy. We conclude this review with further discussion regarding the potential for combining fMRI and iEEG techniques in future investigations of memory function.

Keywords: fMRI; Functional magnetic resonance imaging; iEEG; Intracranial electroencephalography; Epilepsy; Brain mapping; Memory; Memory system; Memory function; Episodic memory

1. Introduction

Our abilities to recall the people, places, and events of our lives, to learn new facts and skills, and to reexperience emotions are all subserved by memory systems of the brain. Given the fundamental importance of memory, its neural basis has been studied by investigators in many different disciplines using a wide variety of approaches. Numerous notable neuropsychological studies have focused on patients with focal brain lesions [1]. In particular, patients with epilepsy, such as the famous case of H.M., have provided a unique population in which to study memory function [2]. Insights have also come from specialized cognitive testing that is performed prior to possible surgical resection in patients with epilepsy. Studies based on findings from intracarotid amytal injection testing (IAT or Wada test) and intracranial electroencephalography (iEEG) have provided unique opportunities to examine the functioning human brain.

In addition to such studies in patients, there are now a number of noninvasive or minimally invasive brain mapping methods useful in the study of memory. Memory studies may now be performed in healthy subjects as well as in epilepsy patients using techniques that are relatively new and unexplored. These techniques include positron emission tomography (PET), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and functional magnetic resonance imaging (fMRI). Each brain mapping modality offers different strengths and weaknesses in terms of spatial and temporal resolution, repeatability, and invasiveness [3–5].

Combining techniques that are complementary with respect to strengths and weaknesses will likely yield the most accurate and useful information regarding the neural correlates of memory. For example, the whole brain coverage of fMRI could be integrated with the fine temporal resolution

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of iEEG to gain more insight into memory processes than could be offered by either technique alone. This integration could be facilitated with frameless stereotactic neuronavigation and the coregistration of respective data sets. As these two different brain mapping modalities depend on different physiological signals, combining them also could allow for the cross-validation of methods [3].

This article reviews the contributions that fMRI and iEEG studies have made to our current understanding of how memory functions arise from the brain. The review begins by summarizing the current classification of different memory systems and their neuroanatomical correlates, focusing on episodic memory and evidence from lesion studies. We then survey both fMRI and iEEG studies of memory function. For each modality, we discuss its physiological basis as well as point out key studies in both healthy subjects (fMRI studies) and patients (fMRI and iEEG) that have led to new insights regarding memory. Advantages and disadvantages of each brain mapping modality are addressed. Wherever appropriate, we point out implications that these studies have for the treatment of patients with epilepsy. We conclude this review with further discussion regarding the potential for combining fMRI and iEEG techniques in future investigations of memory function.

2. Memory systems: Classifications, neuroanatomy, and lesion studies

2.1. Classification of memory systems

Memory systems of the brain record, retain, and retrieve experiences, facts, knowledge, and skills that form an essential framework for our thoughts, emotions, and behavior. Schacter and Tulving define the term *memory system* as simply a way for the brain to process information that will be available for use at a later time, with or without conscious awareness [1,6,7]. Multiple memory systems support different behavioral aspects of memory and depend on different neuroanatomical structures [8,9]. While some systems are associated with conscious awareness (explicit) and can be consciously recalled (declarative), others are expressed by a change in behavior (implicit) and are typically unconscious (nondeclarative) [1].

Four major memory systems are classified respectively as episodic, semantic, working, and procedural memory. Episodic memory refers to a system that records, retains, and retrieves autobiographical knowledge about experiences that occurred at a specific place and time [10]. This memory system can be assessed in the laboratory using direct tests of free recall, cued recall, and recognition. In contrast, the semantic memory system stores general, conceptual, and factual knowledge that is not related to any specific temporal or spatial context (e.g., the President of the United States) [1,6]. Working memory refers to the ability to maintain and use information that one needs to store temporarily in one's mind. Procedural memory is the ability to learn behavioral and cognitive skills that operate automatically and usually unconsciously. Episodic memory, semantic memory, and working memory are explicit and declarative. Budson and Price argue that procedural memory can be explicit (e.g., learning to drive a car with manual transmission) or implicit (e.g., learning the sequence of numbers on a touch-tone phone without conscious effort), but is nondeclarative [1].

Until around 1980, our understanding of memory systems and their distinct neuroanatomical circuits were based almost entirely on studies of patients with memory deficits due to focal or degenerative brain injuries [11]. Certain lesions produce dramatic memory deficits that provide clues about which brain regions are necessary for specific memory systems. For example, the aforementioned patient H.M. underwent bilateral temporal lobectomy for the treatment of medically refractory epilepsy and has since suffered from severe anterograde and partial retrograde amnesia [2,12]. However, despite his severe declarative memory deficit, H.M. has no impairment in procedural memory or other cognitive functions [2].

2.2. Episodic memory

In this review, we are concerned primarily with the neural substrates of episodic memory; the functional neuroanatomy associated with other memory systems has been reviewed elsewhere [1,6,7]. Many areas of the brain likely contribute to aspects of episodic memory because, in order for memory systems to be engaged, there must be perceptual input and associated processing. Thus, particular domains of episodic memory depend on the integrity of relevant sensory and cognitive systems [13,14]. One may think of memory-specific processing as a late stage in the hierarchical processing of any internal or external stimuli. While many perceptual and association areas may be recruited during memory encoding or retrieval, the areas *essential* for the memory processes constitute only a subset of those regions. Much theoretical and experimental work has focused on finding the biological basis of specific episodic memories, i.e., the engram [15].

The neuroanatomical model for the actual encoding and retrieval of episodic memory has been the subject of many research efforts. Based on lesion studies, areas within the medial temporal lobe (MTL) are vital for encoding information in its spatial and temporal context. Furthermore, the prefrontal cortex interacts with the MTL at different levels, in both encoding and recall stages of memory processes [16].

2.3. Lesion studies of the medial temporal lobes

The MTL memory system itself consists of the hippocampal structures (the CA fields, the dentate gyrus, and the subiculum); the nearby perirhinal, entorhinal, and parahippocampal cortices; and the amygdala [17,18].