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Review

Temporal lobe epilepsy as a model to understand human memory: The distinction between explicit and implicit memory

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Abstract

Decades of research have provided substantial evidence of memory impairments in patients with temporal lobe epilepsy (TLE), including deficits in the encoding, storage, and retrieval of new information. These findings are not surprising, given the associated underlying neuroanatomy, including the hippocampus and surrounding medial temporal lobe structures. Because of its associated anatomic and cognitive characteristics, TLE has provided an excellent model by which to examine specific aspects of human memory functioning, including classic distinctions such as that between explicit and implicit memory. Various clinical and experimental research studies have supported the idea that both conscious and unconscious processes support memory functioning, but the role of relevant brain structures has been the subject of debate. This review is concerned with a discussion of the current status of this research and, importantly, how TLE can inform future studies of memory distinctions.

Keywords: Temporal lobe epilepsy; Anterior temporal lobectomy; Explicit memory; Implicit memory; Associative memory; Relational memory; Hippocampus; Medial temporal lobe

1. Introduction

Memory impairment in patients with temporal lobe epilepsy (TLE) is well-documented. Due to the relatively circumscribed nature of epilepsy-related pathology, which typically involves cell loss and gliosis in the hippocampus and surrounding structures in the medial temporal lobe, TLE has provided an excellent model by which to investigate specific aspects of the learning and retrieval of new information. This has allowed not only for a better understanding of the role of medial temporal lobe structures in memory, but has also provided a clearer picture of the memory deficits that specifically characterize patients with TLE. Of particular relevance has been the role that TLE has played in helping to parse out the different systems that have been posited to underlie human memory, and to further clarify the underlying anatomy. Establishing relationships between memory systems and underlying anatomy has been a key feature of contemporary memory research. The current review is concerned with a classic distinction in the memory literature, that between explicit and implicit memory.

We begin with a brief review of common memory distinctions, including a discussion of the basic themes underlying each definition. Next, we review the literature on explicit and implicit memory, including a discussion of findings in patient populations, and concluding with a summary of the current status of the distinction and its relevance to memory research. We then briefly discuss brain structures involved in TLE and their relation to the specific cognitive processes underlying both explicit and implicit memory. Lastly, we specifically discuss the explicit and implicit memory deficits that have been reported in TLE,

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and we then provide some insights into future research on memory distinctions in this patient population.

2. Memory distinctions

2.1. Brief overview

For years, memory researchers have relied on the use of the conceptual classification of memory distinctions to better understand normal and abnormal human memory functioning. Such distinctions have been particularly helpful when characterizing particular neuropsychological disorders, in which impairment is often seen in one memory-related domain but not in another. Consistent reports of these dissociations have led to the development of such terms as *declarative versus nondeclarative memory, declarative versus procedural memory, episodic versus semantic memory*, as well as *explicit and implicit memory*. Fig. 1 is a diagram containing brief descriptions of these classifications and illustrating the theoretical relationships between them.

The underlying conceptual themes behind each dissociation overlap to some extent, and as such, many patient groups who demonstrate deficits in one category also do so in another (designated in the figure by the depiction of categories with overlapping constructs). For example, under the rubric of declarative memory, episodic memory and explicit memory both refer, in some degree, to the acquisition of new information, and memory-disordered patients typically have difficulty across tasks ascribed to each of these domains. Implicit memory and procedural memory, as well as implicit memory and semantic memory, also contain similar definitions, and researchers often interchange these terms when referring to learning under unconscious or "indirect" means (as in the case of implicit memory and procedural memory), or when referring to the access of memory stores that are not tied to a particular event, place, or time (as in the case of semantic memory). In this review, we highlight the distinction between explicit and implicit memory, a dissociation that has received much attention in neuropsychological research. Many experimental tasks have successfully dissociated performance in different patient populations, including neuropsychological disorders such as amnesia and Alzheimer's disease, as well as developmental stages such as aging. Because of its direct relevance to patients with temporal lobe memory disorders, we focus solely on the class of implicit memory known as indirect memory, which includes tasks such as repetition or associative priming (see Fig. 1). Often, researchers interchange the term *implicit memory* with *priming*, which refers to the speeded processing of a stimulus as a result of prior exposure to or familiarity with that stimulus. We do not discuss procedural memory (also known as implicit skill or motor learning) or semantic memory as part of the review.

2.2. Implicit and explicit memory: Definition of the distinction

The distinction between explicit and implicit memory has been a dominant theme in memory research over the past several decades. In this article, we define *explicit memory* (also referred to as *direct memory*) as the intentional recollection of newly learned information. Thus, we refer to the recall of episodic information, such as that which is acquired during the study, or learning, phase of a memory experiment. Critical to this widely used definition is the idea that explicit memory involves the retrieval of material that has been recently introduced to memory stores. Such information may include facts and specific events, but does not include information that is not tied to a specific context or that is considered "general knowledge" (semantic mem-

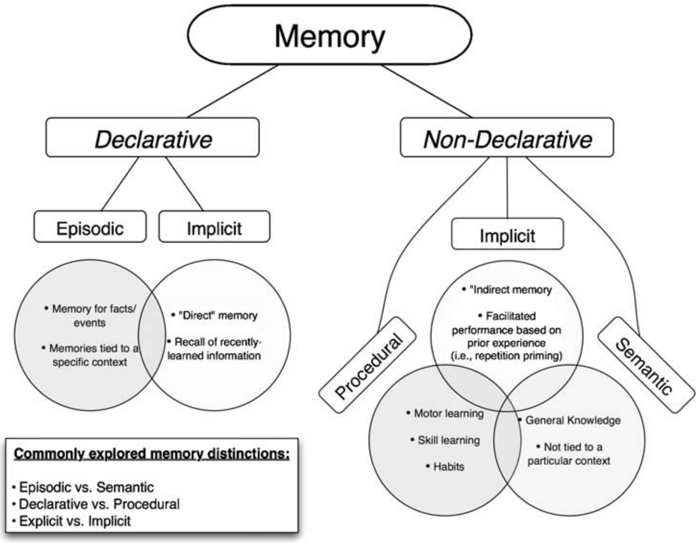

Fig. 1. Classification of commonly studied memory categories and distinctions. Overlapping circles indicate partially overlapping constructs underlying each category.

ory). In the past, explicit memory has typically been measured using standard direct tests such as free recall and recognition [1,2]. We define *implicit memory* (also occasionally referred to as *indirect memory*) as the unconscious or unintentional remembering of material that was previously seen or learned. According to this definition, implicit memory is manifested in facilitated performance (increased accuracy, reduced perceptual thresholds, decreased reaction time) when studied material is later represented, even in situations where no direct reference is made to the original learning episode. Examples of such indirect tasks fall under the rubric of "repetition priming," and include word-stem completion [3,4], lexical decision [5], and perceptual identification [6]. Interestingly, manipulations of encoding, in which to-be-remembered material is studied elaboratively (deep encoding) rather than nonelaboratively (shallow encoding), enhance explicit, but not implicit, memory [6–8]. However, altering variables such as the modality of presentation (e.g., auditory presentation during study and visual recognition at test) has been shown to adversely impact implicit, but not explicit recall [7,9,10]. These observations, which have been recorded extensively over the past several decades, have led to the belief that explicit and implicit memory may rely on different underlying brain systems [2,11–15]. Data collected on patients who have circumscribed damage to memory-related brain regions (such as the hippocampus and medial temporal lobe) have supported this idea; such patients fail at tasks of explicit memory (such as free recall or recognition) while showing normal or near-normal performance on tests of implicit memory (such as word-stem completion and reaction time measures that assess memory indirectly) [1,16]. Importantly, recent cognitive neuroscience investigations using advanced technology such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) have demonstrated distinct functional anatomic and electrophysiological signatures for tasks that engage conscious versus unconscious aspects of memory [17–19], providing evidence for separate underlying "explicit" and "implicit" systems.

Despite the findings suggesting that explicit memory and implicit memory are mediated by distinct underlying neurocognitive and anatomical systems, there is also a substantial amount of evidence to refute this idea. One popular alternative account has suggested that explicit memory and implicit memory tap different cognitive processes (i.e., conceptual versus perceptual processing, or recollection versus familiarity) mediated by one distributed memory system. This view posits that explicit memory depends primarily on effortful, conceptual processing, whereas tests that are more sensitive to implicit memory tend to draw more heavily on noneffortful, perceptually-based or data-driven processing [6,20,21]. Current conceptualizations of this theory have referred to the distinction between recollection (the specific remembering of an explicit or episodic event) and familiarity (a nonspecific feeling of occasion of remembrance) as the key element in the explicit–implicit dichotomy. Thus, this theory, which has typically been referred to as the "processing account," is more focused on cognitive processes, as opposed to anatomical correlates. In response to the debate over these two aforementioned views and to the fact that data supporting either one are extremely mixed, other theoretical interpretations have developed that essentially contain aspects of both. A "hybrid" view that has gained popularity indicates that brain regions and cognitive processes recruited by explicit and implicit memory are not mutually exclusive of one another (i.e., both may be recruited on a given task), but that to some degree, each is subserved by different and possibly separate underlying cognitive and anatomical systems that are differentially active in conscious/deliberate versus automatic retrieval modes [1]. Thus, functions within the two domains are not stochastically independent of one another.

2.3. Implicit memory: Novel versus preexisting information

In the quest to understand cognitive and neuroanatomical aspects of implicit and explicit memory, it became clear that by itself, implicit memory was not as straightforward as it was once thought to be. In early research, much of what constituted evidence of implicit memory involved facilitation of memories or memory representations that were familiar (already in memory) at the time of learning. For example, showing faster reaction time to the second presentation of the word *nurse* in a lexical decision task was dependent on the prior existence of the *nurse* word form in memory, and was thought to represent the "activation" of that word by the learning phase. What would occur if subjects were taught to remember novel information (e.g., novel associations such as "mother–calendar") not previously existent in memory? Would they show implicit memory for these associations? More recent research with amnesic patients has demonstrated deficits on implicit tests that assessed memory for new (as opposed to familiar) material, and that the degree of such a deficit was in proportion to the severity of amnesia [22]. These findings have led to the idea that implicit memory can be further divided to distinguish memory for "preexisting" (i.e., familiar) versus "novel" (i.e., new) material. One important question concerns whether these two types of implicit memory are functionally and anatomically distinct from one another.

Preexisting or familiar material includes examples such as real words and semantic associations between words (such as nurse–doctor), and is thought to exist in long-term representational memory stores prior to the start of an experiment or a recollective event. In contrast, novel material is broadly defined as information that is introduced to memory for the first time in an experiment (i.e., in a study phase) [23]. Examples have included nonwords and new associations between previously (i.e., preexperimentally) unrelated words. The fact that patients with documented explicit memory impairments also show deficits on tests of novel, but not preexisting memory has revealed that perhaps implicit memory is not as immune to the impact of brain injury as once believed. This finding, initially revealed in amnesic patients, has been replicated in other patient groups who have damage to medial temporal lobe structures as a hallmark disease feature. For example, Fleischman et al. have reported on several occasions that patients with Alzheimer's disease (in which pathology initially involves the transentorhinal cortex and hippocampus) are unable to learn new associations between words explicitly or implicitly, despite normal or near-normal performance on implicit tasks of familiar material [24,25]. More recently, Yang et al. reported impaired priming of new associations in patients with circumscribed medial temporal lobe damage, in addition to impaired explicit recall of these same associations. This finding supports the belief that the hippocampus is involved in memory for recently learned associative material, even when assessed in an indirect, or implicit, manner [26].

3. Anatomical correlates of explicit and implicit memory

For years it has been widely accepted that the hippocampus and medial temporal lobe (MTL) play a key role in the complex neural system important for declarative, or explicit, memory [2,16,27,28]. Evidence from a wide variety of neuroimaging and cognitive studies with both healthy and memory-disordered populations has supported this view [16,29,30]. However, the intact performance of amnesic patients on tasks of implicit memory has led to the general conclusion that under certain conditions, amnesic patients are able to access newly learned information. At one time, these results were taken as evidence that implicit memory is not dependent on medial temporal lobe structures typically damaged in these patients. As described above, these results led researchers to believe that the mechanism underlying priming for preexisting material may involve mere activation of a memory representation resident in neocortical brain regions. Such "reactivation" of memory traces is independent of the hippocampal system [1,13]. Functional imaging studies have supported this general conclusion; a fairly consistent finding has been that explicit and implicit memory tests result in different patterns of activation [19,29,31,32]. Activations in the hippocampal system (including entorhinal and parahippocampal cortex) occur during explicit memory tasks such as free recall and recognition, while certain tasks of implicit memory result in activations within occipital and occipitotemporal cortex [31,33,34]. Buckner et al. studied the differential activation of free recall (explicit measure) and word-stem completion (implicit measure) using positron emission tomography [29]. Results demonstrated that while free recall consistently resulted in increased blood flow to the medial temporal lobe and hippocampus, the implicit measure caused increased blood flow only in posterior regions of the occipital cortex.

Despite this evidence, the idea that certain types of implicit memory may be differentially dependent on structures such as the hippocampus and MTL raises the question as to whether these brain regions are exclusively important for explicit memory and to what degree they may be critical for the indirect acquisition of new memories. One of the main functions of the hippocampus during memory encoding is in binding unrelated items together to form a meaningful unit, often referred to as *relational processing* [35–40]. This becomes particularly important when more complex associations have to be made both within and between items. For example, remembering a single word, while still requiring some degree of relational processing, is theoretically less taxing on the hippocampal system than remembering two words together in association [36]. The ability to mnemonically process increasingly complex stimuli is directly proportional to the integrity of the hippocampus [41,42]. Along these lines, there is also evidence that the hippocampus and adjacent MTL structures become more important in processing stimuli that require more elaborative, or conceptual, processing [42]. Martin reported increased medial temporal activity following deep (elaborative) rather than shallow (nonelaborative) processing, providing support for this theory. Additionally, greater activation was found in medial temporal regions following exposure to *novel* as opposed to *familiar* stimuli [43]. This finding is consistent with the idea that the hippocampal complex plays a significant role in novelty detection [44–46], regardless of whether the task is explicit or implicit. Taken together, these findings suggest that the hippocampus may also be important for forms of implicit memory in which stimuli are novel or unfamiliar to existing memory stores.

There are also a number of findings that support the idea that the hippocampus is especially important for binding unrelated elements together to form a direct association. Chun and Phelps report that amnesic patients with hippocampal damage are impaired in the implicit learning of contextual visual material, suggesting that the hippocampus is important for the binding together of multiple pieces of information, even in an unconscious, indirect manner [47]. Neuroimaging in healthy control subjects has also provided support for this notion. In an fMRI study that specifically examined associative versus item memory, Giovanello et al. reported that the hippocampal formation is more engaged for associative material, suggesting that the hippocampus may be particularly involved in relational processing [48]. A more recent article reported that an amnesic patient with selective hippocampal damage was more impaired on associative than item recognition, providing further support for this idea [49]. However, this particular study also demonstrated that familiarity based judgments, which theoretically do not involve conscious recall [50], were relatively intact, again suggesting that extrahippocampal regions of the MT are sufficient to support certain types of memory. Other studies have reported that certain regions of the MTL, including the hippocampus, may be involved more generally in tasks that contain a highly contextual or conceptual component [51], meaning they are more challenging and taxing on the memory system.

Broadly speaking, it appears that in hippocampally damaged subjects, deficits are more prominent when the memory task involves associative information, suggesting that the hippocampus becomes critical for integrating new information, especially as the complexity of the memory increases. In individuals with normal hippocampi, perhaps those structures will support indirect aspects of memory, albeit implicitly. However, when the hippocampus becomes damaged, learning and retrieval may operate differently, from both a cognitive and a neuroanatomic perspective. To the extent that there are resources to compensate for damage, certain aspects of memory may be supported, but such compensation may be limited if the task requires this critical associational component that only the hippocampus can provide. In other words, impairments may be more salient as incoming information becomes more complex and requires more extensive binding of multiple cues.

4. Current status of the distinction between explicit and implicit memory: Applicability to patient populations

The historical process of classifying memory systems such as explicit and implicit memory has been challenging, as it becomes increasingly difficult to place new data at either end of the dichotomy. In a recent review, Squire proposes that the debates over characterizing memory systems, such as the explicit/implicit distinction, are rooted in a more universal scientific mission to understand more clearly how exactly the brain acquires, stores, and retrieves new information [52]. Work conducted in patient populations has supported the general idea that there are different forms of consciousness that are differentially affected by disease or damage. What predicts specific impairments, however, has been perhaps the most puzzling, as one group of patients with MTL damage can often perform quite differently than another group on virtually identical experimental tasks [3,53,54]. One hypothesis to explain such differences suggests that performance is based, at least in part, on the severity and extent of damage of MTL structures [22]. This idea was made especially plausible in a review conducted by Gooding et al. in 2000, which found that in amnesic patients, severity of impairment on explicit and novel implicit memory measures was directly related to the extent of lesion [22]. An alternative, or perhaps additional, explanation relates to the type of material involved when assessing explicit and implicit memory for novel versus preexisting information. Yang et al. reported deficits only on novel implicit tasks that required forming new associations in memory [26]. In their study, patients who sustained damage to MTL regions actually performed normally on tasks that indirectly assessed learning and memory for single-item information (such as a single word), but demonstrated impaired performance on measures of both explicit and implicit memory for new associations between words. A more recent study reported impaired explicit and implicit memory for novel between-word associations in patients with MTL amnesia and, importantly, found that degree of priming correlated directly with the degree of episodic memory impairment (established through performance on standardized neuropsychological memory tests) [55]. This general finding has been documented elsewhere [48], leading to the conclusion that to-be-remembered material requiring an associative or relational component is more vulnerable to the effects of MTL damage, regardless of the direct (explicit) or indirect (implicit) nature of the task. In fact, the role of the hippocampus in relational aspects of memory is a dominant theme in contemporary memory research [56–58], and recent cognitive–neuroanatomic studies have focused on the hippocampus as critical for encoding relational aspects of incoming information, regardless of the explicit or implicit nature of the task. However, this idea has been refuted in the literature. Rosenbaum et al. reported that the amnesic patient K.C., who has extensive bilateral hippocampal loss, was able to demonstrate implicit associative priming for new associations [59]. The authors argued that MTL structures external to the hippocampus can be involved in the binding together of incoming, unrelated information. Despite this, it is also important to note that some amnesic subjects, such as K.C., may have adapted to their deficits over time and, thus, have essentially "learned" to use extrahippocampal brain structures when engaging in experimental memory tasks. Although it is certainly not "normal," it nonetheless is enough to support certain types of memory encoding and retrieval. Thus, the degree to which hippocampal function contributes to performance on a memory task depends on a multitude of factors, including type of material to be learned or remembered [22], severity of damage [60,61], duration of disease or impairment [62,63], and which remaining brain structures are available [55,59].

Experimental explicit and implicit tasks also have varying learning and retrieval demands, making it difficult to compare performance across studies. It is also challenging to ensure that a nominally "indirect test" is free of "explicit contamination," or to prevent participants from unknowingly engaging in explicit strategies despite indirect instructions and procedures. This latter problem has plagued the explicit/implicit debate since the distinction was first introduced, and has only been partially resolved. An additional criticism relates to the idea that differences across implicit memory studies can be attributed to the fact that results from implicit memory tasks, and specifically, repetition priming measures, are considerably less reliable than are those from explicit memory tasks. More specifically, indirect memory tests have been criticized as being unreliable estimates of implicit memory functioning. However, a recent review refutes this idea, asserting that reliability is similar across implicit and explicit tasks [64]. It is likely that the processes underlying implicit and explicit memory are not stochastically independent of one another, and because implicit memory reveals more variability, it is likely that functions underlying implicit tasks are more heterogeneous. However, the robustness of the distinction between explicit and implicit memory is fairly powerful, and has been observed across several patient groups, including amnesics, patients with early Alzheimer's disease [65], aging patients [66], and patients with epilepsy [67], all who commonly share damage to MTL structures as a defining feature.

Interestingly, there is no evidence of a reverse dissociation in patients with MTL damage; to our knowledge, there is no existing report of impaired implicit but intact explicit memory, in the context of the definitions we describe here. That is, there are no findings suggesting impaired repetition priming for relational information in the face of intact explicit memory for this same material. Thus, inferences of a distinction between explicit and implicit memory, and between implicit memory for preexisting material and that for novel material, are based solely on single dissociations, which are considerably less powerful than double dissociations [68]. For example, evidence of impaired priming of single-item stimuli in the face of intact memory for associative information would argue more strongly for the view that a true cognitive and neuroanatomic distinction exists between these mnemonic properties. This has important implications when arguing for and using the explicit/implicit distinction in both experimental and clinical research. In an effort to integrate the varying results across studies and across patient populations, we propose a model that explains our view of how different components contribute to various aspects of explicit and implicit memory. In addition, this model provides an illustration of why only single dissociations are observed when evaluating this distinction (see Fig. 2).

We depict explicit and implicit memory on a continuum of dependence on the hippocampus, as well as of the degree of effort/intentionality underlying each task. To make this depiction clearer, we also list tasks that lie at different points on the continuum. It should be noted that within each task, the level of complexity may vary with respect to stimuli that either are novel or require a more associative component (as in an unrelated word pair), compared with stimuli that are item-specific or are theorized to have preestablished representations in memory; relational information is more difficult to encode and remember than single items. According to the overall model, hippocampal involvement is less critical as the continuum progresses from explicit to implicit memory. Thus, the hippocampal complex is most important for the explicit, intentional recall of complex information (top of the model, for example, free recall of previously learned unrelated word pairs), but becomes less taxed as retrieval is less effortful and more "indirect" (bottom of the model, for example, tasks that are based on memory for preexisting, item-specific information such as repetition priming of single words and mere perceptual priming). The model provides an illustration to suggest that the hippocampal complex is important, albeit to varying degrees, for the laying down of new memories, regardless of the direct or indirect nature of the task. This model is in contrast to views stemming from decades of

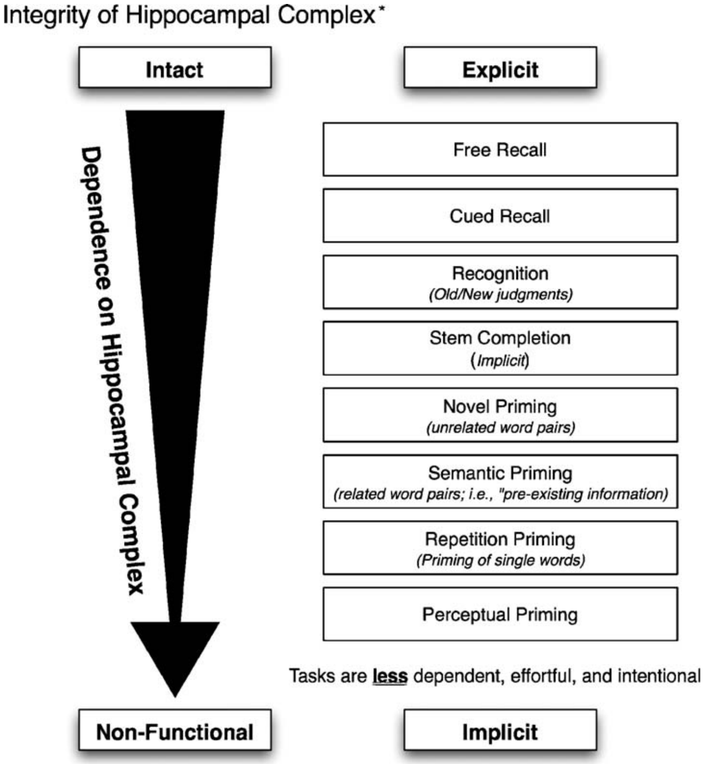

Fig. 2. Hypothesized continuum of explicit and implicit memory as it relates to hippocampal involvement and degree of effort and intentionality. In this model, *hippocampus* refers collectively to the hippocampal complex, which includes the hippocampus and surrounding MTL structures and cortices (parahippocampal gyrus, preirhinal and entorhinal cortex).

amnesia research, which state that the hippocampus is important for explicit but not implicit memory.

Our model also serves to explain why only single dissociations are observed in explicit/implicit memory studies, and also brings a partial resolution to the question of why findings are so variable, especially at the far right of the continuum. It suggests that the failure to learn new information is based in large part on the degree of involvement required by the hippocampal system; this, in turn, is related to the overall degree of MTL damage. Because this damage is variable across individual patients and patient groups, its differential impact on task performance is likely inconsistent as well. On tasks that are less reliant on the integrity of the hippocampal system, individual variability is likely to be more prevalent, as possibilities such as functional brain reorganization are more likely to have an effect. However, on more hippocampally dependent memory measures, there is less allowance for involvement of other brain regions or cognitive processes such as this, and as a result, performance across groups is more consistent and predictable.

5. Epilepsy as a model for studying dissociations such as explicit and implicit memory

The neuroanatomical focus of TLE has made it a particularly appropriate model for the study of memory. Due to the fact that seizures stemming from the temporal lobe tend to result from relatively focal lesions, regions including the hippocampal complex and surrounding cortices are fairly consistently affected. Additionally, TLE is often associated with regional atrophy to such areas, seen as mesial temporal or Ammon's horn sclerosis, which specifically involve portions of the hippocampus. Technological advances such as surgery, fMRI, EEG, and other various electrophysiological techniques have allowed for careful investigations of the neural bases of TLE, and have added more generally to the literature on epilepsy and memory. For example, such studies have concluded that patients with TLE have impaired long-term potentiation, a neural process that is critical for the laying down of new traces in memory [69,70]. In recent years, anterior temporal lobectomy has become a common and effective treatment for patients with intractable complex partial epilepsy of temporal lobe origin. Evaluation of patients from the viewpoint of cognitive neuroscience provides a unique opportunity to study the effect of epilepsy on memory functioning. In addition, research with surgical epilepsy patients has also allowed for pre- and post-operative neurocognitive investigations as a way of further understanding the functional memory capacity of resected brain regions and for investigating reorganization of function in the brain after surgery.

6. Memory deficits in TLE

As described in the previous section, epilepsy has a predilection for specific brain regions, with the seizure foci often located within the critical memory structures of the MTL. Although there is remarkable consistency in the brain regions impacted by TLE, the severity of damage and the interruption of the normal functioning of these brain structures may vary considerably across patients. The functional integrity of these brain regions can be affected by a number of disease-related variables. For example, the age at disease onset [71–74]; the severity, frequency, and type of seizures [75,76]; lateralization of seizure foci; and the effect of seizure medication [77] have all been linked to memory and cognitive changes in patients with epilepsy. These aspects of TLE have been discussed in detail elsewhere and, therefore, are not reviewed here. In general, these disease variables contribute to the functioning of the MTL in isolation and in combination. As a result, there is variability in both the neuroanatomical correlates and cognitive deficits observed in patients with TLE.

Given the significant impact of epilepsy on MTL memory structures, it is not surprising that patients with TLE experience greater memory impairments compared with patients with extratemporal or generalized seizures [78]. Despite the variability of neuroanatomical changes associated with TLE, specific memory deficits are commonly observed in these patients. Memory deficits are so common, in fact, that many standardized measures of memory make specific mention of TLE in their manuals. In general, an association of laterality of seizure foci and material-specific deficits is often noted, with greater verbal impairment associated with foci in the left temporal lobe and greater nonverbal memory impairment associated with foci in the right temporal lobe. Across studies, however, there is great variability and less consensus associated with the relationship between right foci and nonverbal memory [79–82].

Jones-Gotman et al. provided a review of the clinical memory measures employed in presurgical evaluation of patients with epilepsy [83]. They described the most consistently reported relationship as that between impaired declarative verbal memory and left temporomesial function in patients with TLE. Lacritz et al. investigated performance on the Wechsler Memory Scale III (WMS-III) subtests in patients with TLE evaluated presurgically [84]. Material-specific deficits were noted, with impaired story learning and story recall (Logical Memory subtest) in patients with left TLE compared with both the normative sample and patients with right TLE (who performed within the average range). In contrast to the verbal learning and memory deficits of the left TLE group, both the left and right TLE groups performed within the impaired range on a measure of nonverbal learning and memory (Visual Reproduction subtest), and both patient groups demonstrated retention rates slightly lower than that of the normative sample. Similar findings of material-specific deficits associated with left seizure foci, but not right, have been reported by Naugle et al. [82]. Performance on the WMS-III, in general, indicates poorer memory performance in patients with TLE compared with the general population, and greater memory impairment in those with left TLE [85]. Barr et al. reported that roughly 30% of patients with TLE experienced nonverbal memory impairment on the Brief Visuospatial Memory Test—Revised (BVMT—R), although this measure was not accurate at lateralizing seizure focus [86].

The majority of studies investigating memory in patients with TLE have focused on anterograde (i.e., recent or explicit) memory. Fewer studies have investigated retrograde memory deficits or memory for remote (i.e., personal historical or general historical/news) events. Patients with TLE may experience difficulty with remote memory associated with years of seizure activity and anterograde memory impairment. Impaired encoding and learning over the years likely result in poor memory for events during that time. A temporal gradient of retrograde amnesia in patients with TLE has been demonstrated by Barr et al. [87] and Seidenberg et al. [88]. Lah et al. investigated recall and recognition of autobiographical and public knowledge in patients who had undergone anterior temporal lobectomy (ATL) [89]. Defective recall of famous public events was observed for both the groups with left and groups with right seizure foci, and the left seizure group also experienced impaired recall of famous people's names. Performance on famous public events did not improve with multiple-choice measures, although improvement with multiple-choice tasks was observed for retrieval of famous names. These researchers reported an infrequent incidence of temporal gradient retrograde memory deficits. Their findings indicate significant retrograde, as well as anterograde, memory deficits in TLE.

Early investigations of the risk of memory decrements following unilateral temporal lobectomy (e.g., surgical resection of the epileptogenic foci) highlighted the importance of considering the capacity of the contralateral temporal lobe and hippocampal complex (i.e., nonresected) to support memory functions. This model of *functional reserve* was highlighted by Penfield and Milner in their description of two patients with significant memory deficits following temporal lobectomy [90]. They suggested that postsurgical deficits may occur in situations in which the nonresected (contralateral) temporal lobe was dysfunctional. In the case where a large portion of the remaining contralateral temporal lobe tissue is sclerotic or dysfunctional, the surgery may have, in effect, resulted in a bilateral temporal lobectomy.

According to Chelune, consideration of the functional reserve of the unresected tissue is essential in avoiding global amnesia in patients undergoing temporal lobectomy, although it may not be as useful in predicting memory deficits in patients with milder, less extensive neuroanatomical damage [60]. A model of *functional adequacy* was offered by Chelune to account for the commonly observed finding of greater memory deficits following temporal lobectomy. This model emphasizes the importance of considering the functional integrity of the tissue to be resected and its contribution to memory. In support of this model, Trenerry et al. noted an inverse relationship between hippocampal atrophy and postsurgical memory decline (less decline after removal of atrophied tissue) [92]. The models of functional reserve and functional adequacy, independent of their role in predicting postsurgical outcome, fit well within our model of memory. The integrity of both the left and right hippocampal complex together, regardless of seizure foci, contributes to memory performance.

7. Explicit and implicit memory in TLE

As has been seen in other populations with damage to the MTL, the examination of explicit and implicit memory in TLE has been a fruitful undertaking, and has given us considerable insights into the characteristic memory disorder. In patients with TLE, direct and indirect memory abilities were first examined in the famous patient H.M., who underwent bilateral hippocampal resection for surgery relief. Gabrieli et al. found that despite showing impairments on explicit tasks, H.M. was able to show intact priming for dot patterns, demonstrating a dissociation between implicit and explicit memory, and suggesting that perhaps some types of learning or acquisition can be done in the absence of a hippocampus [33]. However, to date, there have been relatively few studies that have specifically examined explicit and implicit memory in patients who have unilateral TLE or have undergone ATL. In 1994, Zaidel examined these abilities in patients who had undergone left or right ATL using a classic direct test (explicit recall) and a classic indirect measure (stem completion). Performance on these measures was then correlated with neuronal density data from resected hippocampi. The authors reported worse explicit memory in patients who had undergone ATL than in those who had undergone right ATL, consistent with the idea that structures within the left MTL are important for verbal memory [93]. However, there were no differences between sides (left versus right) on tasks of implicit memory. Interestingly, only indices of implicit memory correlated positively with hippocampal cell density [93]. These data were interpreted to reflect the fact that the left hippocampus is critical for verbal aspects of memory, regardless of the conscious (explicit) or unconscious (implicit) nature. A follow-up study [67] examined explicit and implicit memory in pre- and post-surgical patients with TLE. In the first experiment, postsurgical explicit and implicit memory scores were examined; results were similar to the authors' previously reported findings [93] and revealed significant left- versus right-sided differences for explicit but not implicit memory. Additionally, they found significant correlations between cell density and implicit memory performance for both left and right hippocampi, but found no such association between cell density and explicit memory. The second experiment in this study focused only on explicit memory for related and unrelated word pairs, taken from a standardized memory measure (WMS-III, Verbal Paired Associates subtest). Performance on pre- and postsurgical tests was examined together in conjunction with morphological hippocampal data; results revealed significant positive correlations between memory performance for the unrelated word pairs and neuronal density only on the left side, indicating that greater cell density was associated with a larger difference between pre- and postsurgical memory scores. Interestingly, scores for related word pairs failed to correlate with cell density, suggesting that the hippocampus is not necessary to retrieve well-learned associations, which is information theoretically presumed to exist in semantic memory stores, even during an actual memory experiment. Collectively, data from these experiments support the idea that the hippocampus is important for certain aspects of both direct and indirect memory tasks, and that TLE may impair aspects of relational memory, regardless of the explicit or implicit nature of the task. This idea is consistent with a recent study focusing specifically on the relationship between anatomy and performance on neuropsychological measures. Weniger et al. reported that subjects with TLE with extensive MTL damage, including large hippocampal and parahippocampal gyrus lesions, performed worse on tasks that involved the learning and retrieval of associative information [94]. Interestingly, these authors also found that degree of impairment was almost directly related to the actual size of the underlying lesion (calculated as a reduction in volume compared with the unaffected hemisphere), providing support for the previously mentioned idea that degree of associative learning deficit often correlates with degree of anatomical damage [22].

Similar behavioral results were reported by Savage et al. in 2002. They assessed explicit and implicit verbal memory in patients who had undergone left or right ATL; patients who underwent left ATL were preexperimentally determined to have significant memory deficits compared with those who underwent right ATL [95]. Memory for unrelated word pairs was assessed using direct recall (explicit memory) and masked recognition priming (implicit memory). The authors argue that, in contrast to tasks such as stem completion, their masked recognition paradigm provides a technique in which awareness of the relationship between test and study material is minimized, thus allowing for a purer estimate of implicit memory. Results revealed that the patients who had undergone right ATL outperformed those who had undergone left ATL on both direct and indirect measures of learning [95]. Similar to the Zaidel studies [41,101], these findings provide support for the idea that relational memory is affected by MTL damage, regardless of whether it is assessed in an explicit or implicit manner. This study also provides evidence that left ATL impairs new learning when compared with right-sided surgery, which is consistent with the general finding that the left MTL is preferentially involved in verbal memory. However, one methodological issue is worth mentioning. In all three of the aforementioned studies, the implicit memory measure was administered *after* the explicit measure, allowing for the possibility that explicit memory may have contaminated the results of the implicit task. That is, either knowingly or unknowingly, participants may have recognized a connection between the tested and previously studied material, thus potentially confounding the results.

A more recent study investigated explicit and implicit memory using a procedure that is designed to reduce the potential for explicit contamination on implicit tests by separating out conscious and unconscious processes. In 1991, Jacoby proposed that the cognitive processes of memory recollection (explicit memory) are fundamentally different from those that underlie mere familiarity (which we have described as an element of implicit memory) of to-be-remembered information [96]. By developing a task that dissociates recollection and familiarity, he created another means by which researchers can investigate the independent role of these processes in memory. Del Vechhio et al. examined implicit and explicit verbal memory in patients with left TLE using Jacoby's "process-dissociation" procedure [97]. When compared with controls, patients with epilepsy performed worse on portions of the task designed to assess explicit memory, but groups performed similarly when assessing implicit memory. These results are in contrast to those reported by Zaidel [67,93] and by Savage et al. [95], and suggest that at least where recollection and familiarity are concerned, most forms of verbal implicit memory in patients with left TLE do not rely on MTL structures.

In general, there have been even fewer studies in TLE that have concentrated more specifically on aspects of implicit associative or conceptual memory, and virtually none that have examined the ability of patients with TLE to demonstrate implicit memory for novel material. In a hallmark study with patients with TLE, Blaxton examined perceptual versus conceptual priming, focusing on the ability to learn contextual information (e.g., semantic cued recall and "general knowledge" facts or statements) versus information that can be learned by simply processing the to-be-remembered material in a data-driven or perceptual manner (e.g., word-fragment completion or graphemic cued recall) [21]. Thus, she investigated these concepts using tests that tapped either explicit or implicit retrieval. She found that regardless of the type of test (implicit or explicit), patients with left TLE were differentially impaired on tasks that were conceptually driven, indicating that it was the processing demands of the test that dictated performance. Importantly, however, implicit tests were administered after the explicit ones, again rendering interpretation somewhat blurred. In a more recent study, Billingsley et al. used this same dichotomy to examine explicit and implicit memory in patients with TLE [98]. Specific tasks included implicit tests of word identification and word generation, as well as explicit tests of recognition and recall; conceptual or perceptual processing was emphasized during encoding/study. Results revealed no differences between the TLE and control groups on tasks of either conceptual or perceptual implicit memory. However, groups did differ on recognition and recall (explicit), with the TLE group demonstrating worse performance. These findings are therefore in contrast to those reported by Blaxton [21], and suggest that structures in the left MTL may not be necessary to support implicit memory or conceptual priming. Importantly, these authors administered the implicit portions prior to the explicit tests, and reexamined results according to subjectively reported awareness of a relationship between test and study for the implicit tasks. Because of this, these results may be a more accurate reflection of pure implicit or indirect learning. It is also worth noting an additional aspect of this study: left and right TLE groups included children, adolescents, and adults, with the total group ranging in age from 9 to 60. Although there were no differences between groups with respect to critical variables such as age at seizure onset, this is an extremely wide range, and it is unknown to what degree neurodevelopmental factors influenced the results in complex ways. As suggested by the authors, the basic underlying cognitive–neuroanatomical structure may be altered, especially in younger patients with TLE or in those with seizure onset during critical developmental periods.

8. Implications and suggestions for future research

Clearly, the distinction between explicit and implicit memory is a complicated one, evidenced by decades of research with healthy participants and with specific patient populations. Over the years, TLE has provided a unique opportunity to study aspects of memory that have been theorized to depend on MTL structures. A review of previous work that has specifically examined explicit and implicit memory in this patient population reveals a mixed picture, with respect to both the status of conscious (explicit) and unconscious (implicit) memory processes and the status of relational, associative, or contextual memory. One reason explaining the complexity of explicit and implicit memory relates to the fact that there are a host of experimental and disease-related variables that can affect response and interpretation of any particular measure. These inherent issues then present limitations to generalization and collective inference making. Despite these concerns, the careful examination of aspects of explicit and implicit memory in TLE has the potential to provide even more insights into the specifics of the memory disorder associated with the disease. Based on what is known about the role of MTL structures in forming new associations, it may be that even in patients with TLE with severe explicit memory impairments, the ability to form new memories, albeit implicitly, remains intact to some degree. However, the question remains: How can further work on this distinction inform both research and clinical work with TLE patients? One avenue we propose is to design more large-scale studies that directly compare the performance of patients with TLE with that of anatomically relevant populations such as MTL amnesics, from which the majority of our current knowledge of the implicit/explicit distinction has arisen. In addition to similar neuroanatomical disease foci, a major advantage to this comparison lies in the fact that the heterogeneity of TLE is similar to that typically seen in amnesia; both groups carry comparable issues such as varying duration of disease, varying age at onset, and, importantly, variable degrees of damage to MTL and hippocampal brain regions. As a result, both groups likely have similar learned compensatory strategies, including the potential recruitment of other brain regions. These similar "confounds" in interpreting results render more accurate cross-study generalizations about the impact that different degrees of hippocampal damage have on direct and indirect memory abilities, and about the role of the hippocampus in explicit and implicit memory. By designing studies with tasks similar to the ones we present in our proposed model, such comparison studies could potentially provide some resolution to questions about the reasons for performance variability at the "top" of the continuum. Ultimately, this work will be able to provide important insights into how MTL structures are affected by disease and how the human memory system can adapt over time.

Another important avenue that we suggest for future research is to take advantage of the burgeoning growth of the bridging of neuropsychological research with cognitive neuroscience techniques, such as fMRI. Based on the principle that an increase in neural activity is accompanied by increases in local blood oxygenation, certain fMRI techniques allow for the direct comparison of stimulus-specific responses with regional brain activity, providing unique opportunities to correlate behavioral performance with underlying brain function. Over the past decade, there have been numerous studies demonstrating the utility of fMRI in both healthy participants and patient groups. Such investigations have also provided support for theories of localization of specific memory functions [99–101]. Use of fMRI in patients with TLE is especially relevant to this issue, as it allows for a more accurate determination of the contributions of other brain regions (i.e., as a result of functional cerebral reorganization) when engaging in direct or indirect memory tasks. This knowledge could then shed light on issues regarding variability in performance, which are particularly relevant as the continuum progresses from explicit to implicit memory.

These advantages also have important clinical implications. In fact, fMRI has potential for regular use in clinical settings, and many epilepsy clinicians have suggested that fMRI replace existing procedures designed to prevent postoperative aphasia or amnesia in patients with TLE who are candidates for temporal lobectomy surgery. The current "standard," the intracarotid sodium amytal test (IAT), is invasive and is associated with risk, and lacks the specificity (i.e., spatial and temporal resolution) of fMRI [102]. Several epilepsy centers have successfully demonstrated that fMRI is a safer and more precise method of determining functional lateralization of brain function. For example, Golby and colleagues report that in eight of nine patients with TLE, fMRI data were consistent with those obtained via the IAT [102]. Even more critically, the fMRI procedures were able to more specifically ascribe encoding abilities to the left or right temporal lobe. This latter finding is especially relevant, as it suggests that fMRI may be able to parse out the differential contributions of separate brain regions for explicit and implicit memory tasks in patients with TLE, potentially rendering performance more specifically predictive of memory abilities following ATL.

Perhaps, in the future, experimental investigations of the explicit/implicit distinction can be translated into clinical practice, with the primary goals of more specifically characterizing the memory deficits that plague the TLE population, as well as informing clinical decision making and treatment planning. An initial step is to incorporate the idea behind implicit memory measures into the traditional neuropsychological workup often used to determine candidates for ATL. In general, the utility of indirect memory measures in routine epilepsy evaluations (either presurgical or postsurgical) is unknown, as currently, most standardized memory measures do not contain implicit components, mainly due to lack of normative data. However, many clinicians do integrate basic underlying theoretical constructs; for example, typical memory examinations include differentiating between recall and recognition, processes that map onto cognitive processes such as recollection and familiarity (see Fig. 2). For example, it would be interesting to specifically examine how implicit memory performance maps onto the model that we propose, and how processes at either end of the continuum operate in the same way as traditionally measured explicit memory. It may be that presurgical memory performance on implicit measures can enhance and even make more accurate predictions regarding postsurgical impairment, especially when combined with sophisticated techniques previously discussed, such as fMRI.

Lastly, it is important to at least briefly discuss the challenging question of using experimental data from studies of explicit and implicit memory to inform treatment or intervention options. Obtaining a better understanding of the memory abilities that operate under intentional or unintentional conditions can have important implications for cognitive rehabilitation strategies, such as memory training and memory rehabilitation. This endeavor, which involves the bridging of research and clinical data, is a challenging yet promising one. One such strategy, errorless learning, is a memory rehabilitation technique shown to improve patients' explicit memory abilities by relying on implicit memory [103]. Numerous studies have demonstrated that several patient groups who are impaired on explicit memory tasks are able to learn new information by being prevented from making mistakes [104,105]. More recently, Page et al. showed that amnesic patients with impaired explicit but intact implicit memory showed an errorless-learning advantage when acquiring new material, suggesting that preserved memory abilities were adequate enough to enable new learning, albeit in a more structured, "training" environment [106]. The fundamental concept behind errorless learning is routed in early work with animals [107] and is based on the idea that making an error reinforces an incorrect response because the lack of explicit memory prevents an individual from remembering the appropriate answer. The prevention of errors therefore forces reliance on implicit memory. Given the fact that this particular technique has demonstrated effectiveness in memory-disordered patients, it may be a worthwhile strategy to attempt in patients with TLE who exhibit deficits in memory. From a broader perspective, the underlying idea that preserved memory abilities can be used to capitalize on improving acquisition or encoding is potentially an important avenue for future clinical and research work in TLE. Regardless of the fact that individual patients may vary with respect to which point on the "continuum" (Fig. 2) memory abilities are impaired, using intact aspects of implicit memory may be effective in enhancing memory retention.

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