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Review

Temporal lobe surgery and memory: Lessons, risks, and opportunities

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ABSTRACT

Careful study of the clinical outcomes of temporal lobe epilepsy (TLE) surgery has greatly advanced our knowledge of the neuroanatomy of human memory. After early cases resulted in profound amnesia, the critical role of the hippocampus and associated medial temporal lobe (MTL) structures to declarative memory became evident. Surgical approaches quickly changed to become unilateral and later, to be more precise, potentially reducing cognitive morbidity. Neuropsychological studies following unilateral temporal lobe resection (TLR) have challenged early models, which simplified the lateralization of verbal and visual memory function. Diagnostic tests, including intracarotid sodium amobarbital procedure (WADA), structural magnetic resonance imaging (MRI), and functional neuroimaging (functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT)), can more accurately lateralize and localize epileptogenic cortex and predict memory outcomes from surgery. Longitudinal studies have shown that memory may even improve in seizure-free patients. From 70 years of experience with epilepsy surgery, we now have a richer understanding of the clinical, neuroimaging, and surgical predictors of memory decline—and improvement—after TLR.

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1. Introduction

Memory dysfunction is the chief cognitive complaint in temporal lobe epilepsy (TLE) [1] with some degree of impairment in most patients [2,3]. Refractory TLE is associated with progressive memory impairment [4–11]. These patients may be outstanding candidates for epilepsy surgery, which offers a potential cure for seizures and further memory decline. Careful longitudinal studies of patients with TLE before and after resective surgery have accelerated our understanding of the neuroanatomy of human memory [1]. Neuropsychology has been established as a fundamental tool for monitoring outcome and quality measures after epilepsy surgery [12].

What kinds of memory decline do patients with TLE suffer? Patients with TLE typically report problems with declarative memory (see Box 1), which is memory that can consciously or explicitly communicated to others [13] and includes episodic and semantic memory [14]. Episodic memory, a term coined by Endel Tulving, involves personal events embedded in a spatiotemporal context [15]. Active retrieval of an episodic memory includes using the content of the event to retrieve specific details such as when and where the event occurred, its emotional valence, and other individuals present. Episodic memories are autobiographical in nature and constitute a form of mental time travel in which we can recover the associated context of the event [16]. Episodic memories can include the vivid recollection of the family members, food, and atmosphere of a holiday celebration; what we remember about yesterday's lecture and speaker; and where we placed our keys this morning. Semantic memory concerns factual knowledge about the world, which is accumulated over time but informs present understanding. Examples include knowledge of public, historical events; object concepts including sensory properties, names, and functional uses; and scientific facts, numbers, and mathematical equations. Semantic memory has been studied through probing recall of famous public events or people to determine if a temporal gradient in retrospective memory decline exists [17,18].

Among patients with unilateral mesial TLE, patients with high seizure burden demonstrated greater anterograde episodic memory impairment. Both patients with high and low seizure burden had poorer retrograde memory for autobiographical episodes and public events memories compared with healthy controls [19]. The dissociation between these cognitive phenotypes suggests differing neuroanatomical substrates for these memory categories. The structure–function relationships can be further tested by examining the cognitive outcomes from this unique set of well-circumscribed surgical "lesions" [20].

This paper reviews TLE surgical cases and postoperative cognitive outcomes, followed by presurgical diagnostic assessments to improve lateralization and localization of the seizure onset zone, and predictors

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Box 1
Overview of Memory Types. Adapted from Markowitsch, H.J. Chapter 4: Memory and Amnesia. In Principles of Cognitive and Behavioral Neurology. Second Edition. Ed. M. Marsel Mesulam.

Type of memory	Definition	Everyday examples	Neuropsychological tasks
Declarative memory	• Memories that consciously or explicitly encoded and retrieved • Dependent on the limbic system, until consolidated		
Semantic Memory	• Knowledge of public events, concepts, and ideas that are acquired over a lifetime • Shared knowledge	• Language learning • Knowledge of famous people, places, and historical events	• Visual (object) naming • Vocabulary • Famous Face Recall
Episodic Memory	• Autobiographical memory for a personally experienced event with an awareness of temporal and spatial context	• Knowledge of route to school or work • Names of friends and colleagues • Memory for special occasions	• Word List Learning • Figure Copy
Nondeclarative or implicit memory	• Information that may be acquired or retrieved without conscious awareness • Can affect behavior • Inferred through better or faster performance		
Priming	• Information recognition based on prior exposure, in the absence of conscious awareness	• Recognizing a child's cry	• Conceptual Priming • Perceptual Priming
Skills/Habits	• Learning or perceptual and motor skills	• Learning to ride a bike or drive a car • Typing on a keyboard	

of memory decline after surgery. We review how surgical techniques have become more precise, to potentially reduce postsurgical cognitive deficits. Finally, we survey postoperative cognitive outcomes, with an emphasis on what temporal lobe resection (TLR) has revealed about the neuroanatomy of memory.

2. Early lessons on memory loss after medial temporal lobe resection

Insights into the neuropsychology of memory have been informed by cognitive changes after surgery. The first epilepsy surgery was performed in 1886 in the United Kingdom by Horsely and MacEwen in collaboration with Hughlings Jackson [21]. These pioneering surgeries involved the identification and removal of lesions in 3 patients with epilepsy. The earliest surgeries for TLE, performed by Penfield and Jasper in Montreal and Bailey and Gibbs in Chicago, avoided the medial temporal lobe (MTL). Kluver and Bucy's monkey experiments showed significant behavioral decline with bitemporal lobe resection [22]. After the role of MTL in seizure networks was identified in the 1950s, surgeries often included the MTL. At the time, the function of the hippocampus and associated structures was poorly understood.

The cognitive catastrophes suffered by several patients who underwent MTL resection in the late 1950s revealed the essential role of the hippocampus and neighboring cortical areas in memory [23]. These early disasters fostered the development of diagnostic tests to better localize seizure focus and cognitive function, to improve surgical outcomes, and to reduce memory impairment. In parallel, cognitive neuroscience and experimental animal studies more precisely defined the neuroanatomy of different memory systems.

Case H.M. revolutionized our understanding of human memory. In 1953, the neurosurgeon Scoville performed a bilateral MTL resection on Henry Molaison (HM), a man with normal intelligence but with medication-refractory seizures. The resection included "the anterior two-thirds of the hippocampus and hippocampal gyrus bilaterally, as well as the uncus and the amygdala." Previously, Scoville performed similar surgeries on patients with schizophrenia to reduce their psychosis but did not adequately assess their postoperative memory. Careful study of HM's cognitive function revealed that a significant reduction in seizures cost him the ability to form new, stable memories [24,25].

While Scoville and neuropsychologist Milner initially thought that this was a pure anterograde memory deficit [25], further study revealed that episodic autobiographical memory was also impaired for events occurring during the prior year to surgery [26]. H.M. had relatively preserved semantic memory for vocabulary, object, and factual knowledge acquired before surgery. Episodic memory for public events before surgery was also intact, as was recognition memory [27]. His personality, social skills, and intelligence appeared unchanged [25]. Implicit learning, including priming and acquiring new motor skills, was also preserved [28].

Even after death and over 60 years after his surgery, H.M.'s case still generates new insights in the neuroanatomy of memory [24]. Immediately post mortem, several 3 Tesla (T) and 7 T magnetic resonance imagings (MRIs) revealed that H.M.'s lesion was not purely hippocampal as once thought, but included the medial temporal cortex, piriform cortex, entorhinal cortex, anterior parahippocampal gyrus, most of the amygdala, perirhinal cortex, and subiculum; and only the anterior half of the hippocampus [29]. Autopsy confirmed that H.M. retained a significant amount of hippocampal tissue. However, most of the entorhinal cortex was removed bilaterally, thereby deafferenting the remaining hippocampus. Thus, extensive bilateral medial TLR, not selective hippocampal damage, resulted in his significant episodic memory deficit [30].

Penfield's surgical cases in the 1950s demonstrated that even unilateral TLR could severely harm memory. One patient who underwent left anterior TLR, including the anterior half of the hippocampus, experienced severe anterograde memory deficits similar to H.M. [31–33]. The patient had semiology, scalp electroencephalogram (EEG), electrocorticography, and intraoperative cortical stimulation that supported seizure onset from the left temporal lobe. However, autopsy later demonstrated right-sided hippocampal sclerosis. Reevaluation of the preoperative EEGs showed one seizure with ictal spread from the right temporal lobe to the left [33]. Thus, a unilateral temporal lobectomy caused a near-global amnesia because of inadequate cognitive reserve of his remaining temporal lobe [24,31].

Scoville and Penfield's surgical cases offered early lessons into the importance of the hippocampus and related MTL structures for declarative memory function. The ability to form new declarative memories (both episodic and semantic) was affected, while sparing memory for prior semantic knowledge. The ability to learn new motor sequences remained intact. Penfield's case emphasized the need to assess the functional reserve of the contralateral MTL [34]. Further, effective surgical therapy depends on accurate lateralization and localization of the epileptogenic cortex. Presurgical testing has evolved in response to these early instructive cases to improve seizure focus localization and reduce the risk of postoperative cognitive deficit.

3. Dominant temporal lobe resection produces a decline in verbal memory, but there is significant variability in cognitive outcomes

Unilateral TLR is an effective therapy, resulting in seizure remission in up to 80% of patients with refractory TLE [35]. However, surgery risks further memory impairment. While not resulting in the profound

amnesia that bilateral MTL resection produced, memory often declines after surgery.

The material-specific model of memory, developed by Milner and colleagues at the Montreal Neurological Institute [36], proposed that left (or language-dominant) and right (or nondominant) temporal lobes process verbal and nonverbal material differently [36]. Verbal memory impairment is observed in patients with left TLE, which can further decline with resection. Conversely, nonverbal memory declines with nondominant TLR, although this finding has been inconsistent and less robust [37]. Nevertheless, this simplistic model continues to influence presurgical decision-making and interpretation of postoperative outcomes today [1,38,39].

The material-specific model's predictions for verbal memory decline are generally supported by large, observational studies. In a meta-analysis of neuropsychological outcomes after temporal lobe surgery, Sherman et al. [40] reported that 44% of patients with a left TLR had verbal memory decline, at twice the rates for patients with a right TLR (20%). Rates of verbal memory decline have varied from 30 to 60% for left (speech-dominant) Anterior temporal lobectomy (ATL) [41,42].

However, the material-specific model's predictions for nonverbal memory decline have been variably supported by the evidence. In a meta-analysis, visual memory declines after left- and right-sided surgeries at equal rates (21% and 23%, respectively) [40]. Visual memory outcomes after right TLR depend on the cognitive task, demonstrate small effect sizes, and are inconsistent [43]. Barr has proposed that visual memory must be conceptualized – and tested – as a dorsal (where) stream and ventral (what) stream [37] to more precisely capture the memory deficits in nondominant TLE.

These heterogeneous findings led to a critical reappraisal of the material-specific model of memory [39]. Saling proposed that verbal and visual memory should not be considered to be unitary constructs and strictly lateralized to dominant and nondominant lobe. Instead, performance must be considered in light of the specific task demands. For example, different tasks of verbal (episodic) memory (e.g., list learning, prose recall) place differing demands on prior semantic knowledge. Confrontation naming (i.e., Boston Naming Test) is a verbal naming task, but objects are presented visually to the subject. The ability to name the object likely depends on familiarity with its sensory and functional properties. Thus, neuropsychological tests are not purely verbal or visual tasks but entail complex demands on episodic memory, semantic knowledge, and visual or auditory processing. These considerations may explain why decline after unilateral TLR is highly variable across patients, and why nondominant TLR produces inconsistent cognitive outcomes. Saling argued that we must disambiguate the medial versus lateral contributions to memory tasks [39].

Patient characteristics also contribute to variable cognitive outcomes. The degree of existing neuronal loss in the left hippocampus predicts worse performance in a verbal episodic memory task of unrelated word-pair associates [44–46]. A structurally intact hippocampus predicted greater functional decline after surgery [47,48]. In other words, removal of an atrophic, sclerotic hippocampus is less likely to result in significant memory decline, compared with a removal of a healthy, functional hippocampus [1]. Patients with little or no hippocampal sclerosis undergoing left anterior temporal lobe resection (ATLR) demonstrated approximately 35% decrease in long delay memory (as measured by the California Verbal Learning Test or CVLT) after surgery. In comparison, patients with sclerotic hippocampal tissue experienced little decline after surgery [1]. Consistent with these imaging findings, patients with better preoperative memory and language performance experienced greater memory decline after left TLR compared with those with worse preoperative performance [34].

Finally, some variability in the magnitude of decline likely results in difference in surgical technique, which can differ by surgeon and center. Overall, larger left TLRs result in worse verbal memory [49,50]. For example, after accounting for baseline performance, the extent of left parahippocampal resection accounted for 27% of the variance in short delay free recall on a word list task, while the extent of left entorhinal resection accounted for 37% of the variance in performance [20].

4. Modern presurgical assessments to localize seizure onset zone and assess the risk of memory decline

Since scalp EEG, electrocorticography, and even intraoperative stimulation could not always localize seizure foci or identify the risk of postoperative cognitive impairments [33], other assessments were needed. These assessments aimed to lateralize memory and language, and also test the cognitive reserve of the cortex contralateral to the planned resection.

4.1. Intracarotid sodium amobarbital procedure (WADA) test

In 1948, Wada performed an intracarotid artery (ICA) injection of sodium amytal (amobarbital) to study the epileptic discharges across hemispheres. He serendipitously founded a test to lateralize speech and memory as injecting via the dominant hemisphere's carotid artery transiently impaired ipsilateral cerebral hemispheric function. In 1960, he demonstrated that amobarbital injections accurately lateralized speech and language function, by correlating with postsurgical outcomes [51].

Milner, Rasmussen, and Branch [52] first used the amobarbital test to assess hippocampal function contralateral to the probable temporal resection. Patients were presented with drawings of objects before unilateral ICA amobarbital injection. A few minutes later, if the patient failed to spontaneously recall the objects, recognition memory was probed [52]. Since the amobarbital procedure anesthetizes the brain regions supplied by the middle and anterior cerebral artery ipsilateral to the injection, failure to recall or recognize the presented items suggested inadequate functional reserve of the contralateral MTL. Temporal lobe resection ipsilateral to injection would likely impair postoperative memory [53].

Routine intracarotid sodium amobarbital procedure (WADA) testing has declined since the 1990s [38]. While the WADA obtained gold-standard status in assessing lateralized material-specific memory outcomes, recent studies demonstrated that baseline neuropsychological evaluation, structural imaging, and neuropathology effectively predict quantitative postoperative memory status [54], with the WADA making little or no independent contribution [34,55–58]. Despite these criticisms, the amobarbital test remains the only functional test to assess each hemisphere's individual contribution to memory [59].

4.2. Structural neuroimaging

Brain MRI, developed in the 1980s, can identify structural lesions causing epilepsy. Concordance of MRI lesion with ictal EEG onset predicts seizure freedom in most cases [60]. Early low-resolution MRI scans were more sensitive than computed tomography (CT). Among 48 patients with TLE, 71% had abnormal 0.5 T MRI scans while only 17% had abnormal CT scans. The MRI at 0.5 T correctly identified all patients with large structural lesions, including arteriovenous malformations, gliomas, hamartomas, and meningioangiomatosis [60]. High-field 3 T and 7 T MRI has further increased our ability to identify epileptogenic lesions. Three Tesla MRI is more than twice as likely to identify epileptogenic lesions than 1.5 T MRI [61] and provides greater resolution of the gray-white junction. Seven Tesla MRI identified focal cortical dysplasias and malformations of cortical development in 23% of patients with epilepsy who were MRI "negative" on 1.5 T or 3 T scans or in those with suspected dual pathology (i.e., a structural lesion in addition to mesial temporal sclerosis) [62].

Further, 0.5 T MRI can identify more than 75% of patients with severe neuronal loss and gliosis of the mesial or lateral temporal lobe and half of all patients with mild to moderate mesial or lateral temporal lobe neuronal loss and gliosis [63]. Hippocampal atrophy and T2

hyperintensity on 0.5 T MRI correlate with hippocampal sclerosis verified with pathology [64]. Identification of hippocampal sclerosis remains an important biomarker for lateralization and localization of epileptogenic networks, as well as predicting memory outcomes.

4.3. Functional neuroimaging

Since the 1990s, measurement of brain activity during cognitive and motor tasks has supported presurgical planning. Functional MRI (fMRI) maps cortical function by identifying regions of increased neuronal activity and coupled blood flow during cognitive tasks, measured as the blood-oxygen-level-dependent (BOLD) contrast between the task and rest condition. Compared with the amobarbital test, fMRI is noninvasive, less expensive, and possesses finer spatial resolution. However, because regional blood flow changes happen over seconds, fMRI lags behind the temporal resolution of EEG or magnetoencephalography (MEG), which can detect changes occurring over milliseconds [65].

Compared with the amobarbital test, fMRI has concordance rates of 86–91% for language lateralization [66,67], with better sensitivity for right hemispheric language function [67]. Discordant findings between fMRI and WADA are a reflection of language lateralization by fMRI as a continuous variable rather than as a binary function (left versus right hemisphere) [68]. Functional MRI allows calculation of relative language dominance expressed as the laterality index from −1 for pure right-sided dominance to +1 for pure left-sided dominance [69].

Functional MRI can also assess brain areas involved in memory tasks, to predict memory outcomes following surgery [55,70,71]. Patients with greater left frontal and anterior hippocampal activation, during a word-encoding task, had greater verbal memory decline after left anterior temporal lobectomy. Conversely, patients with left greater than right posterior hippocampal activation had less verbal memory decline [70,71]. Patients with right greater than left anterior hippocampal fMRI activation during a face-encoding task had greater visual decline after right-sided surgery, while posterior hippocampal activation predicted better memory outcome [70]. Left-sided memory lateralization index (LI) was also associated with significant postoperative verbal memory decline [71]. On the other hand, Binder et al. [56] did not find hippocampal LI in a word list learning and delayed recall task correlated with verbal memory outcome; however, fMRI language LI was predictive of decline in patients who received a left ATL. In a series of stepwise multiple regression analysis, Binder et al. found that clinical traits such as preoperative memory score and age at epilepsy onset accounted for approximately 50% of the variance in list learning memory, while the fMRI LI accounted for an additional 10% in list learning outcome. In their model, WADA results did not improve the predictive power of the model [56].

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are imaging techniques that can improved localization of seizure onset zones. Positron emission tomography and SPECT use radiolabeled probes whose emissions are detected by the scanner. 18 F-2-deoxyglucose-PET (FDG-PET) uses radiolabeled glucose or oxygen to assess areas of altered metabolism or blood flow in the brain [72]. The PET glucose ligand has a half-life of 110 min and assesses interictal blood flow patterns [73]. Gaillard et al. [74] used interictal PET to show that patients with TLE have decreased interictal glucose metabolism in the ictal onset temporal lobe. Positron emission tomography was more sensitive in patients with MRI abnormalities, correctly lateralizing seizure onset zone in 87% of cases with MRI lesions and only 60% of cases without lesions [75].

The SPECT ligand technetium 99m hexamethylpropylene amine oxime (99m Tc-HMPAO) is rapidly fixed in the brain, allowing the study of cerebral blood flow at the time of injection [76,77]. The majority of the SPECT ligand crosses the blood–brain barrier quickly and becomes trapped within the cell compartment [78]. Peak brain levels of the SPECT ligand occur within 2 min after injection, with little redistribution for at least 2 h, which makes it useful to study ictal blood flow [73]. The SPECT subtraction method compares the ictal to interictal SPECT blood flow patterns to determine the most likely ictal onset zone. Among 35 patients with well-localized TLE, correct seizure onset was lateralized correctly in 89% of patients with ictal SPECT versus 63% with interictal FDG-PET. However, using less strict criteria (i.e., lower level of confidence) for lateralization, there was no significant difference between ictal SPECT (94%) and interictal PET (83%) [75].

In summary, these diagnostic tools have been used to more accurately pinpoint seizure onset zone and predict the risk of memory decline. Regarding the latter, Stroup et al. have found that clinical and imaging data, including (1) resection of the dominant hemisphere, (2) MRI findings besides unilateral mesial temporal sclerosis, (3) intact preoperative verbal memory performance, and (4) good WADA test performance after injection of the hemisphere contralateral to the seizure focus, predicted memory decline after surgery [58]. Together, these risk factors suggest that the functional and structural integrity of the to-be-resected temporal lobe anticipates postoperative memory impairment [35].

5. Surgical methods have become more selective and less invasive, reducing memory morbidity

Multimodal techniques to improve seizure localization and assess MTL memory function have led to more restricted surgical resections. Penfield and Baldwin [79] performed their *anterior temporal lobectomy* including a sucker to extract the hippocampus and amygdala. They described excisions extending beyond the anterior 5.5 cm causing contralateral superior visual field defects. Falconer [80] modified this procedure using en bloc resection, which enabled better pathological characterization. In 1956, Morris proposed the standard temporal lobectomy including the anterior 6.5 cm of the temporal lobe, the uncus, amygdala, anterior 2–4 cm of the hippocampus, and lateral temporal cortex [81]. The lateral temporal cortex would later be spared by modified temporal lobectomy and selective amygdalohippocampectomy.

In 1984, Spencer, Spencer, Mattson, Williamson, and Novelly [82] found that 20% of patients with TLE had a seizure focus including posterior hippocampus, beyond the limits of the standard anterior 6.5-cm lobectomy but were hesitant to extend the posterior resection margin further because of speech function typically residing in the lateral temporal lobe. Instead, only the anterior 4.5 cm of lateral temporal lobe was resected, which allowed better exposure to resect the amygdala, hippocampus, parahippocampus, uncus, and fusiform gyrus [82].

Selective amygdalohippocampectomy offered a strategy to limit lateral temporal cortex resection. Niemeyer's transventricular amygdalohippocampectomy involved an incision in the second temporal gyrus to access the lateral ventricle and remove the hippocampus and amygdala [83]. Limited data regarding seizure and cognitive outcomes restricted widespread adoption. Later, Wieser and Yarsagil developed the transylvian amygadalohippocampectomy aimed to preserve more neocortex than Niemeyer's original *transventricular amygdalohippocampectomy* [84]. Their small study observed that amygdalohippocampectomy caused less verbal memory deficits than anterior two-thirds temporal lobectomy.

Seizure outcomes in anterior temporal lobectomy and selective amygdalohippocampectomy remain an area of active research. In anterior temporal lobectomy, seizure outcomes depend on the extent of resection and preoperative pathology. Randomized and retrospective studies reveal that anterior TLRs with more extensive hippocampal removal result in twice the likelihood of achieving seizure freedom [85,86]. Anterior temporal lobectomy is more likely to result in seizure freedom if the MRI shows a concordant lesion, such as temporal lobe atrophy, tumor, or mesial temporal lobe sclerosis [85]. Recent studies favor anterior temporal lobectomy over selective amygdalohippocampectomy. While initial studies demonstrated similar rates of seizure freedom after anterior temporal lobectomy and selective amygdalohippocampectomy [87,88], meta-analyses revealed that

anterior temporal lobectomies were more likely to achieve seizure freedom [89,90].

The *Responsive Neurostimulation System* (RNS, NeuroPace) is an United States Food and Drug Administration-approved (FDA-approved) device to detect and treat refractory focal-onset epilepsy using closed-loop electrical stimulation. Patients with refractory focal epilepsy, who are poor candidates for resection due to an overlap between epileptogenic and eloquent cortex, and have one or two seizure foci are ideal RNS candidates [91–93]. The system includes two four-contact leads placed directly on the seizure focus, which record and store changes in local field potentials. Clinicians customize the RNS to detect patient-specific epileptiform activity. Median seizure reduction was 53% 2 years after implantation [94] and 62% after 5 years [91].

Neuropsychological testing of RNS patients reveals no significant cognitive decline at 2 years after implantation [95]. Patients with neocortical seizure onsets were more likely to experience modest improvements in naming, while those who had MTL onsets were more likely to have improvements in verbal learning. The reason for these improvements may reflect reduced seizures or interictal discharges or neuromodulatory effects of electrical stimulation [95].

Laser interstitial thermal ablation (LITT) is a minimally invasive surgery that can treat epilepsy caused by small lesions such as mesial temporal sclerosis, cavernomas, or cortical dysplasias. The procedure utilizes a stereotactically inserted catheter that is then heated with a laser to thermally ablate the surrounding area. Laser interstitial thermal ablation is less invasive, requires a shorter hospital stay, and permits a faster return to normal activities compared with open surgery [96].

Seizure and cognitive outcomes after LITT remain limited by small cohort studies. Among 23 patients with TLE who underwent LITT, 65% remained free of disabling seizures at 1 year, with 73% of patients with mesial temporal sclerosis attaining seizure freedom [97]. Laser interstitial thermal ablation may result in better cognitive outcomes compared with anterior temporal lobectomy, because of smaller volume of tissue ablated. Among 19 patients with TLE who underwent LITT, there was no decline in recognizing or naming famous faces or in naming common nouns, in contrast to 39 who underwent open resection. Left ATLR resulted in impaired naming of famous faces and common objects, while right ATLR impaired face recognition [98]. However, two patients with TLE who underwent LITT showed significant postoperative verbal and visual memory decline with intact naming, visuospatial ability, and attention [99]. Another report of five patients with left TLE who underwent LITT had intact contextual (narrative) verbal memory postoperatively, but three experienced significant noncontextual verbal memory decline as measured by list learning [100]. Available data show that LITT spares semantically loaded memory tasks and naming compared with standard TLRs, but long-term seizure outcomes remain poorly defined and may depend on identification of a single small lesion.

6. Nociferous cortex and possible functional recovery after surgery

The dynamic relationship between seizure burden and memory decline and longitudinal clinical outcomes after surgery has yielded important information. Postoperative cognitive outcomes depend on seizure outcomes. For patients with unilateral TLR, ongoing seizure burden appears to worsen memory, causing a "double jeopardy" [101]. However, patients whose seizures are cured or significantly reduced after surgery may have a long-term cognitive benefit from surgery. These clinical observations illustrate the concept of the "nociferous cortex" and the cognitive impact of ongoing seizures.

6.1. Concept of the nociferous cortex

Nociferous cortex refers to epileptogenic tissue that is dysfunctional in three ways, it 1) is the origin or element in the epileptogenic network, 2) does not perform its normal functions, and 3) impairs the function of other brain areas [102]. Nociferous is derived from Latin *nocere*, to harm.

The first reference to this concept in epilepsy surgery is from Krause and Schum [103], who noted that in some cases of infantile hemiplegia, strength improved after resection of the epileptogenic cortex. In 1950, Welch and Penfield reported that after resection of cortical seizure foci in three patients with hemiplegic cerebral palsy, spasticity was reduced and motor function improved [104]. The first case involved a 22-year-old pathologically left-handed woman who demonstrated right-sided hemiplegia at age one month and developed focal epilepsy at age 11 years. After seizure focus resection involving primary sensorimotor cortex,

> "There was a remarkable change in the patient's hemiparesis. Instead of carrying the paretic upper extremity in a flexed and spastic manner as she had done before, she now kept her arm extended by her side… The muscles were plastic. She was beginning to use the hand for eating which had never been possible before. In walking she could swing her leg without the former spastic stiffness so that her hemiplegic limp had actually disappeared. She had spent the year doing satisfactory university work."

Welch and Penfield concluded that the left postcentral and precentral areas did not support voluntary motor control after the injury and functional reorganization but could still pathologically influence spinal motor mechanisms. Ablation of these injured regions reduced spasticity.

Penfield and Jasper [105] first used the term *nociferous* to describe the dramatic positive transformation of an aggressive boy after hemispherectomy: "Among patients who have large areas of abnormality in one hemisphere, abnormal behavior may appear, together with advancing mental retardation. The behavioral abnormality is often a more important complaint than the seizures themselves. Radical complete excision may correct the abnormal behavior, stop the seizures, and allow improvement in the patient's mental state."

The concept of nociferous cortex has quietly persisted in epileptology, with subsequent studies primarily focusing on cognitive and behavioral outcomes. Of the three tenets to establish cortex nociferous, the first is the most straightforward, demonstrating that a region is the seizure focus or key element in the epileptogenic network. The second tenet, that the region does not function normally, is more difficult to establish. This is supported by 1) neurological deficits concordant with epileptogenic cortex (e.g., left hemiparesis with a right central seizure focus, episodic memory deficit with left mesial temporal sclerosis) or 2) abnormalities in structural (e.g., MRI) or functional testing (e.g., EEG, PET, fMRI, magnetic resonance spectroscopy (MRS), WADA test). Variable degrees of functional reorganization, most prominent with early-life neurological insults or seizure onset, can further confound localization of sensorimotor, cognitive, or behavioral functions. Even with concordant localizing evidence of dysfunction on the neurological examination, structural and functional assessments, residual function in the epileptogenic cortex cannot be excluded. Overall, the greater the preoperative neurological deficit and concordance across structural and functional measures that a candidate region is abnormal and epileptogenic, the more likely that region has little or no function.

The third tenet of establishing nociferous cortex – improved function after resection of epileptogenic tissue – is complex and difficult to quantify. Resection of epileptogenic tissue likely creates both negative and positive functional outcomes. Improvements can occur in motor (i.e., strength, tone, resolution of involuntary movements), cognitive (e.g., attention, verbal memory, executive functions, social language), and behavior (e.g., mood, irritability, anxiety).

Functional studies support that functional recovery can occur removal of nociferous cortex. After successful TLRs, MRI spectroscopy studies revealed that N-acetyl-aspartate levels increase in the contralateral temporal lobe, consistent with improved neuronal function [106–108]. Positron emission tomography studies reveal normalization of glucose metabolism in the ipsilateral and contralateral temporal lobes

[109,110]. Even when functional improvements follow resective surgeries, it can be difficult to disentangle the contributions of altered interictal epileptiform activity, seizures, diaschisis, and antiseizure or psychotropic medications.

6.2. Longitudinal studies demonstrate memory improvement over time in some patients

Cognition after surgery is dynamic and highly variable between subjects. Longer follow-up intervals reveal further decline in some patients and improvement in others. The meta-analysis of postsurgical cognitive status [40] reporting declines in verbal and visual memory also found some gains in verbal memory (7% in left, 14% in right) and visual memory (15% for left-sided, 10% for right-sided). For example, verbal fluency (generating items in a category) generally improved after surgery, with 27% patients with left TLR experiencing gains in verbal fluency compared with 10% experiencing losses [40].

Long-term postsurgical memory outcomes may differ depending on the timepoint of assessment after surgery. Studies investigating the long-term follow-up followed patients from 2 to 10 years after surgery. Early studies following patients from 2 to 5 years after surgery showed ongoing memory decline in left TLR surgical patients [111,112], including decreases in verbal memory and visual memory between the 1-year and 9-year assessments [42]. Patients who underwent left TLR experienced decline in the word-pairs delayed recall task, which is sensitive to left hippocampal integrity [48,113]. Patients with right TLR and a nonsurgical control group had verbal and visual memory declines.

Recent European longitudinal studies demonstrated cognitive stability or even improvement after temporal lobectomy [114–116]. Immediate decline in verbal memory observed within 2 years after dominant TLR was stable at 10 years [114,115]. By contrast, nondominant temporal lobectomy resulted in a positive trend in verbal memory after 2 years. A large European study found that improvements in memory were more common in younger patients who were seizure-free or had reduced drug load [116].

These differences in longitudinal outcomes have been attributed to differences in patient populations (including age), differing surgical techniques, and variable patient attrition (with patients who are doing poorly more likely to continue to follow at a tertiary care center) [116]. Further, if cognitive outcomes stabilize 1–2 years after surgery, then measurement at 1 and 10 years may mistakenly suggest ongoing cognitive decline.

While there are few pediatric studies with children, evidence supports favorable cognitive outcomes after surgery. Gains in language performance and attention occur postoperatively regardless of the side of surgery. Memory performance improved if surgery resulted in seizure freedom [117]. After TLR, children may recover from postoperative impairment within the first year of surgery [118]. Conversely, ongoing seizures after TLR are associated with declines over time [116].

Together, longitudinal studies suggest that if nociferous cortex is removed, cognitive gains are possible. These improvements in verbal and visual memory are associated with seizure freedom after surgery and suggest that functional recovery is possible. These positive effects may be mediated by decreased deleterious impact of seizures, interictal discharges, or antiseizure medications. Finally, functional recovery is more common in younger patients [115,116].

7. Summary and conclusions

Careful study of the outcomes of TLE surgery has greatly advanced our knowledge of the neuroanatomy of human memory. After the initial devastating outcomes, the critical role of the hippocampus and associated MTL structures to declarative memory became evident. Surgical approaches quickly changed to become unilateral and later, to be more precise, potentially reducing cognitive morbidity. Neuropsychological studies following unilateral TLR have challenged early models, which simplified the lateralization of verbal and visual memory function. Diagnostic tests can more accurately lateralize and localize epileptogenic cortex, and predict memory outcomes from surgery. Longitudinal studies have shown that memory may improve in seizure-free patients. Seventy years after HM, we now have a richer understanding of the clinical, neuroimaging, and surgical predictors of memory decline—and improvement—after TLR.

Despite these advancements, we still lack reliable tools to accurately predict an individual's long-term potential for functional improvement or decline after resective surgery. Individual traits such as age, focality of seizure onset zone, onset and duration of epilepsy, lifetime generalized tonic–clonic seizures, functional status of the epileptogenic cortex, and resection margins all contribute to seizure and cognitive outcomes, but their relative contributions are not understood. Routine and long-term follow-up after surgery is needed. A model incorporating the likelihood of seizure freedom, early cognitive deficits, and long-term cognitive improvements, for an area of resected tissue would enormously advance epilepsy surgery, as well as our understanding of human memory.

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Declaration of Competing Interest

The authors declare no competing interests.

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