



Comparing the Wada Test and Functional MRI for the Presurgical Evaluation of Memory in Temporal Lobe Epilepsy

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Abstract

Purpose of Review The usefulness of the Wada test (WT) predicting memory impairment from temporal lobe epilepsy (TLE) surgery has been debated, and it has progressively been replaced by functional MRI (fMRI). We review the current role of WT and fMRI in the presurgical assessment of TLE, and how novel surgical techniques might improve cognitive outcomes.

Recent Findings fMRI's ability to predict global amnesia has not been assessed. Although WT can produce false-positive results, it is still indicated in patients at risk for developing global amnesia: those with significant bilateral or contralateral memory deficits. In the current review, WT exhibited no added value, beyond preclinical data, for predicting material-specific memory impairment, whereas fMRI was reliable for either verbal or non-verbal memory decline. Abnormal functional connectivity on resting state fMRI (rs-fMRI) between the posterior cingulate and the hippocampus may be a predictor of postsurgical memory outcomes. Restricted resections to the pathogenic tissue, stereotactic laser, radiosurgery, and SEEG-guided thermos-coagulation were associated with better cognitive outcome.

Summary fMRI should be used routinely in the presurgical workup of TLE to predict verbal and/or non-verbal memory decline, whereas WT may be indicated when there is a high risk of postsurgical global amnesia. Rs-fMRI is a promising tool for the presurgical workup of TLE, and more restricted resections are recommended to enhance cognitive outcomes.

Keywords fMRI · Intracarotid amobarbital test · IAT · Resting state · Temporal lobe epilepsy · Surgery

Abbreviations

ATL	Anteromedial temporal lobectomy
FC	Functional connectivity
fMRI	Functional magnetic resonance
Hc	Hippocampus

mTL	Mesial temporal lobe
MTS	Mesial temporal sclerosis
PCC	Posterior cingulate cortex
PHc	Parahippocampal cortex
Post.	Posterior
rs-fMRI	Resting state fMRI
TL	Temporal lobe
TLE	Temporal lobe epilepsy
WT	Wada test

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Introduction

Temporal lobe epilepsy (TLE) surgery comprises 60–80% of epilepsy surgeries, and accomplishes long-term cure rates in 66% of these cases [1]. However, since mesial temporal lobes (mTL) contain structures vital to memory function, patients frequently suffer declarative memory deficits after surgery, which may adversely affect their quality of life [2]. Therefore, it is an important part of the preoperative workup

to weigh the risks of memory decline against the potential benefits of seizure freedom.

Among the available complementary tests able to estimate postsurgical deficits, the Wada test (WT) has been used for memory lateralization. However, its reliability for this is controversial, and the test has inherent risks due to its invasiveness. Consequently, there has been a considerable effort to find noninvasive methods to replace WT for this purpose, with functional magnetic resonance (fMRI) possessing the greatest potential [3, 4].

In this paper, we aim to review the alterations of memory function in TLE, the risks of memory decline after temporal lobe (TL) surgery, and the current role of WT and fMRI in the presurgical evaluation of TLE patients.

Memory Physiology

Declarative memory refers to facts and events that we can consciously bring to mind. It comprises episodic memory for past experiences, and semantic memory for the meanings of words, objects, people, and emotions [5].

Declarative memory is supported by a large, distributed network of regions across the brain, among which mTL structures, and especially the hippocampus (Hc), are critical [6]. The Hc seems to have mainly an associative function, binding items to their context for construction of scenes that compose episodic recollection [7].

In contrast, item recognition related to familiarity processing may be mediated by the perirhinal cortex [8–11]. Despite the evidence supporting this, the functional division between Hc and perirhinal networks for recollection and familiarity is still debated. Perirhinal cortex and Hc seem to code information differently, with perirhinal cortex more stimuli-specific, while the Hc is more abstract, coding conjunctions of attributes that comprise an episodic memory [12].

Evidence also indicates that the anterior and posterior portions of the Hc form two distinct memory circuits. The anterior Hc is connected to the entorhinal cortex, temporal pole and orbitofrontal cortex, and is primarily involved with scene processing and construction. Meanwhile, the posterior Hc is connected to the posterior parahippocampal cortex (PHc), posterior cingulate, thalamus, and dorsolateral prefrontal cortex, which are mainly associated with spatial locations and context processing [6, 13].

A proposed model for episodic memory suggests that the perirhinal cortex encodes information about items to be remembered, while the posterior PHc stores contextual spatial and non-spatial information [12]. Furthermore, the anterior Hc system provides a route by which emotion can influence declarative memory, via involvement of the amygdala, nucleus accumbens, medial prefrontal, and orbital cortex [13].

Although the anterior Hc system appears to be more involved in verbal episodic memory and the posterior Hc in visual memory [6], the specialization for verbal or non-verbal material rely mostly on the information received from the ipsilateral hemisphere. Consequently, temporal and extratemporal language areas in the dominant hemisphere, usually the left, make the ipsilateral mTL relatively specialized in verbal memory [5, 14•]. On the other hand, connectivity between posterior cortical regions and the non-dominant TL, usually the right, involve the ipsilateral mTL region in visuospatial memory tasks [15–17]. However, this strict view of the classic material-specific model has been weakened, as more cases have emerged documenting postoperative verbal memory decline after a presumed non-dominant right anteromedial temporal lobectomy (ATL) [5]. Concerning the visual domain, the literature rather suggests involvement of both mTLs in visuospatial memory, with dynamic interactions depending on the specific task [15, 18] (Fig. 1).

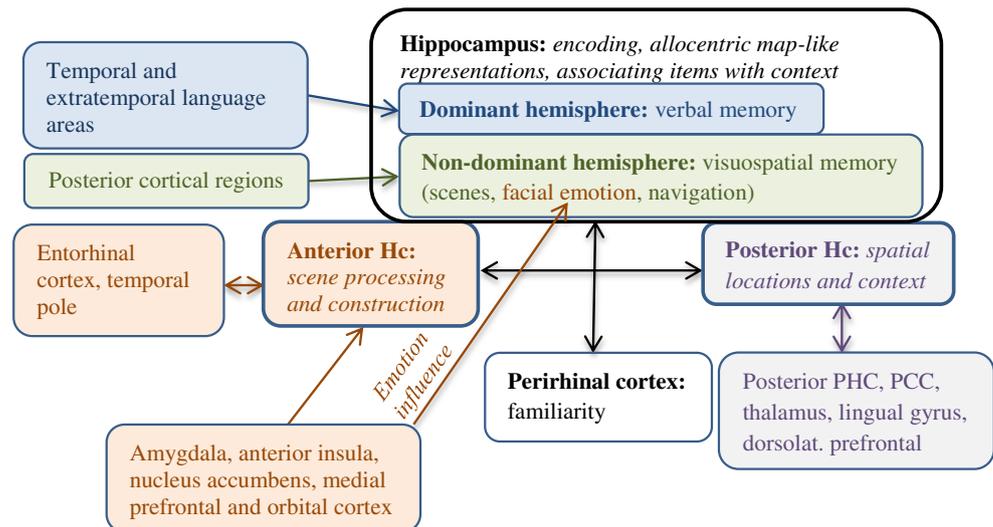
Memory and Mesial Temporal Lobe Epilepsy (mTLE)

Mesial temporal lobe epilepsy is a large-scale network disease, with functional abnormalities extending far beyond the mTL. However, the most commonly affected domains are verbal memory among left mTLE patients and non-verbal memory in right mTLE patients (in up to 69% and 59% of patients, respectively), followed by problems with attention, visuoconstructive functions, and facial-emotion recognition (especially with right mTLE) [19]. The verbal memory impairment in left mTLE patients consists of impaired arbitrary memory (e.g., semantically unrelated word pairs), with relative preservation of semantically structured forms of verbal learning served by the lateral and anterior temporal cortices [20].

A high frequency of seizures has been shown to disrupt the effective connectivity within the TL, resulting in impaired memory and executive dysfunction, and even progressive gray and white matter brain atrophy in some studies [21, 22].

Patients with mTLE present with increased activity in the temporal and prefrontal cortex during acquisition and retrieval [23, 24]. It has also become apparent that mTLE patients tend to reorganize their verbal and non-verbal memory functions to the contralesional mTL [18, 24]; regarding to this, there is evidence of more diffuse and bilateral cortical representation of verbal memory functions in left mTLE, especially in the middle and ventrolateral frontal regions [18]. However, this functional reorganization does not seem to preserve good memory function [25]. Moreover, the epileptogenic Hc tends to alter the structure and function of contralateral mTL cortex, potentially resulting in both verbal and non-verbal memory deficits [6].

Fig. 1 Diagram representing the function and interactions of brain regions involved in declarative memory. Hc: Hippocampus; PCC: Posterior Cingulate Cortex; PHC: Parahippocampus



In this regard, progressive memory decline has been reported in 20–25% of patients with chronic TLE over a 4-year interval, being associated with lower baseline intellectual capacity, the duration of epilepsy, seizure frequency, history of status epilepticus, polypharmacy, and progressive Hc atrophy [21, 26]. However, not all investigators have identified worsening of cognitive performance over time. In one study, cognitive deficits associated with mTLE in childhood remained stable at least until 60 years of age, despite the intractable nature of the seizures [27].

Nonetheless, patients with adult-onset focal epilepsy seem to be at higher risk of experiencing accelerated cognitive aging, especially if there is comorbid pathology (stroke, cardiovascular, metabolic, or inflammatory disease), low educational level, or a previous history of status epilepticus [21, 28]. As with the regular aging process, formal intelligence scores are primarily lowered by a reduced speed in information processing, while higher order functions are preserved [28].

Memory and Epilepsy Surgery for mTLE

Bilateral mTL resection causes severe memory impairment (also called global amnesia) [5], but it is unclear whether such amnesia ever occurs after unilateral mTL resection [29, 30]. All reported cases with severe memory deficits after unilateral ATL had signs of dysfunction in the contralateral Hc [31, 32]. This reinforces the idea that the semantic and episodic memory systems are distributed across both TLs, giving a degree of redundancy that makes them resistant to unilateral damage [5]. Different series have pointed out that the risk of severe memory decline is extremely small (between 0.5 and 1.8%) in modern days when cases are carefully selected after a comprehensive evaluation with EEG and neuroimaging [29, 31].

Conversely, approximately 33–38% of individuals with TLE experience a significant decline from their baseline verbal

memory, and 20% a significant decline in visual learning after surgery [2, 29]. Verbal memory decline is more frequent (44%) in patients who undergo ATL in the language-dominant hemisphere and can be highly incapacitating [33]. This takes the form of poor recall on semantic tasks, such as naming, word-list learning, and short stories, plus non-semantic tasks like semantically unrelated word pairs. Patients with the best memory outcomes are those with impaired preoperative verbal memory in both semantic and non-semantic constituents, since they are most likely to already have damage in the neocortex or adjacent white matter on top of mTL pathology [20, 34]. Studies show stabilization of verbal memory decline 2 years after surgery, without further deterioration at 10 years [19].

Patients undergoing non-dominant language (usually right) ATL are as likely to experience verbal memory decline (sometimes only temporarily during the first 3 months) as verbal memory improvement [29, 35].

Losses in visuospatial memory occur similarly after right (23%) and left (21%) ATL [33]. It becomes manifested by disturbed learning of designs and patterns and musical compositions [19, 33, 34]. Some studies also have revealed larger deficits in face and emotion recognition after right ATL [5].

Finally, extratemporal non-memory functions—like attention, motor function and visuo-construction—tend to improve after ATL on either side [33].

Apart from hemispheric laterality, other factors associated with an increased risk of memory decline after TLE surgery are a later age of seizure onset or neurological insult, high-level memory function, memory deficits during the postictal period, mood disturbances, and the lack of any structural abnormalities in the resected Hc. Persistence of seizures or epileptiform discharges has been associated in some studies with poor cognitive outcomes [23, 36, 37].

Two non-mutually exclusive and probably complementary ways to understand memory changes due to surgery have been

postulated. The *functional reserve model* posits that postsurgical memory outcome depends on the integrity of the contralateral mTL and its ability to support memory functions. Therefore, greater impairment of function in the hemisphere contralateral to seizure focus would imply a higher risk of memory decline. Conversely, the *functional adequacy model* claims that postsurgical memory deficits depend on the integrity of the TL destined for resection, since removing functionally healthy tissue affects memory abilities [38].

Functional MRI studies have demonstrated reorganization of the memory circuits after ATL, with improvements in ipsilateral temporal and frontal lobe functionality. However, the efficiency of this recruitment helping to improve cognitive functions is unclear [24].

Wada Test (WT)

The WT simulates the effects of brain surgery by temporarily inactivating one cerebral hemisphere at a time using amobarbital, a short-acting barbiturate, or some other similar anesthetic agent [39]. The WT was first used by Juhn Wada in the 1950s to identify hemispheric language dominance. In 1962, Brenda Milner and colleagues extended its use to predict postsurgical amnesia [40].

Mechanism

General WT procedures have been detailed in one of our previous publications [3]. The memory evaluation usually follows language testing. Two procedures are commonly used. The first involves presenting several different stimuli to the patient which, after a distractor task is applied, are presented again to see if they are recognized, and to continue to do this until the drug's effect disappears. The second procedure involves presenting a preset number of stimuli and testing how well they are recalled or recognized once the drug's effect has vanished [41].

Multiple types of item are used across centers, including tangible objects, photographs, line drawings of objects, cards with printed words or sentences, and spoken phrases or words. However, encoding of language-based items can be altered by language impairment, introducing a major confounder. Because of this, using stimuli whose registration is independent of language or that can be dually encoded (based on verbal and visual characteristics) is recommended [42, 43].

Limitations of and Complication Rates with WT

Using WT for memory functions has several additional limitations, besides those from WT itself outlined in our previous

publication [3]: First, relevant structures of interest, especially the posterior two thirds of the Hc and PHc, are omitted from the exam, since they are not supplied by the anterior circulation [44]. Hence, a selective WT has been developed, in which barbiturate is injected into the posterior cerebral artery or anterior choroidal artery. This also enables memory testing, while preserving language functions. In addition, the effect of the amobarbital lasts 3–5 min, insufficient time to test memory reliably, especially under the behavioral effects of anesthesia. Finally, neither an optimal WT protocol for memory testing nor a definition of test failure has been developed, and those used differ widely between centers [45].

WT Reliability for Memory Lateralization

Only anecdotal case reports and expert opinions suggest that complete amnesia during WT anesthetization of the hemisphere to be resected contraindicates ATL [30, 31]. Loring and colleagues, for example, described a patient with permanent anterograde amnesic syndrome after right ATL, who recalled none of the eight items presented after right hemisphere injection, but all those presented after the left-sided injection [46]. Among 71 respondents in The Palm Desert Survey in 1993, six indicated having knowledge of a patient who had failed the memory component of the WT and subsequently became amnesic after TL surgery [47].

WT has falsely predicted global amnesia, calling into question its reliability for this purpose [36, 48, 49]. For instance, Loring et al. and Kubu et al. reported 20 patients who failed WT and proceeded to ATL, none of whom became amnesic afterwards [50, 51]. At the same time, many patients are not selected for surgery because they failed the WT for memory, and this practice makes it difficult to know the real risk in this group. In this regard, Rathore published a large series of 116 left TLE-MTS cases, in which no patient was denied surgery on the basis of WT scores if electroclinical, MRI, and neuropsychological data were concordant. There were no cases of postoperative amnesia or even differences in memory outcomes among those who had failed the WT [48].

Limited reproducibility of the WT for memory results has been demonstrated [52]. Stanulis and colleagues reported that 4/180 consecutive individuals performed so poorly on the WT, they required retesting; yet 3/4 passed the repeated WT [53]. Novelty and Williamson reported failure in 25/325 (7.5%) WTs. When the individuals underwent repeat testing using a lower dose of amytal, 21 of these 25 passed and underwent surgical resection without postoperative amnesia [54].

The WT has been used to assess the risk of material-specific (verbal or visuospatial) memory deficits after ATL. In this regard, in 20 left TLE patients, Wyllie et al. observed that those who had $\geq 20\%$ lower score in the ipsilateral WT had a trend towards higher verbal memory deficits after ATL, in agreement with the

functional adequacy model [30]. Similarly, Kneebone et al. reported significant verbal memory decrements in left ATL with good memory performance during contralateral WT [55]. Loring et al. observed a greater decline in verbal memory in 17 left ATL patients with small ipsilateral-to-contralateral WT memory score asymmetries, but not in right ATL, regarding visual memory [56]. In addition, Andelman et al. found increased verbal learning decline in left and right ATL patients with good ipsilateral hemisphere functionality [57].

Other study results have supported the functional reserve theory. Bell et al. found that low functionality during a right-sided WT predicted a greater risk of semantic memory decline in 22 left TLE patients [58]. Chiaravalloti et al. observed that WT total recognition and word memory scores during the ipsilateral injection correlated with postoperative verbal memory decline in 28 left and 42 right ATL patients [34]. Jokeit et al. found similar results in left ATL patients [59].

Combining both functional adequacy and reserve basis, Sabsevitz et al. observed that a reversed WT memory score (better WT memory performance in the hemisphere of surgical interest) was the best predictor of postoperative verbal memory outcome [60]. In contrast, in a large series, Kirsch et al. failed to identify any correlation between WT memory asymmetry and persistent postoperative verbal memory decline after left or right ATL [45].

Few studies have detected any predictive value of WT for visuospatial memory. White et al. found that bilateral failure or low left hemisphere function during WT predicted a decline in Rey-Osterrieth complex figure test scores after left ATL. This finding was unexpected, given that the Rey-Osterrieth test is considered a test of non-dominant hemisphere function [61]. Using a mixture of words, drawings, and faces, LaCruz et al. found visuospatial memory after right or left ATL to be related to presurgical functionality of the contralateral hemisphere [49]. This inconsistency of results regarding WT capacity to predict visual memory outcome is not only attributed to its more bilateral distribution but also to the variety of aspects explored by the different tasks employed (for example, recognition of abstract figures depend on different brain regions than the facial recognition) [34].

Finally, other studies have explored more comprehensive multivariate models for predicting memory outcomes. Baxendale et al. found that WT indices only identified one additional patient at risk of verbal memory decline out of 91 [43]. Similarly, Chelune et al., Stroup et al., and Elshorst et al. found that WT scores did not add significant predictive value for verbal memory decline beyond the sum of hemispheric dominance for language, Hc alterations in MRI, and baseline verbal memory scores [62, 63, 64]. Lineweaver et al. demonstrated that WT only slightly improved the prediction of delayed visual memory outcome (from 78 to 81%) after surgery, compared to standard neuropsychological testing and Hc volumetric analysis [36].

Furthermore, Kemp et al. concluded, after auditing 141 consecutive WT test results, that right-handed patients with right temporal lesions and preserved verbal memory were very unlikely to fail and probably did not need to undergo the WT. On the other hand, patients with left TL lesions were more likely to fail the WT, regardless of their handedness or baseline neuropsychological performance [65].

Finally, a recent meta-analysis by Schmid et al. indicates lower sensitivity, but higher specificity of memory WT, relative to language WT, in terms of predicting postsurgical memory decline [66].

fMRI

As a noninvasive test, fMRI is safer than WT, yields results that are free from the effects of sedation, and costs only a fraction of the WT. Furthermore, fMRI can locate distinct components of the memory-related brain circuitry, and thereby facilitate tailored surgery that avoids relevant eloquent cortex.

fMRI Mechanisms

Functional MRI principles and procedures have been detailed elsewhere [3].

To elicit the activated functional brain areas using the blood oxygen level-dependent (BOLD) signal effectively, most fMRI studies employ a block design, in which stimuli are alternated within rest blocks (rest, task1, rest, task2). Conversely, employing an event-related design, stimuli of different types are randomly intermixed, and only the activation during items successfully remembered are taken into account [4]. Event-related design is considered more specifically focused on the brain processes of interest, but might not result in strong activation and require an additional post scanning recollection phase. On the other hand, the event-related design facilitates anterior Hc activation (the part that will be resected during standard ATL) [67], whereas blocked paradigm stimuli activate more posterior Hc and PHc areas, probably due to greater involvement of visual scene processing [68].

Memory fMRI Paradigms

Initial fMRI studies found hemispheric lateralization to be dependent upon the stage of memory processing, with left frontal and temporal activation during encoding and right frontal and temporal activation during retrieval [69].

However, subsequent studies have demonstrated some degree of material-specific lateralization. For example, Golby et al. found that verbal encoding tasks activated the inferior

prefrontal cortex and the mTL more on the left side, whereas pattern encoding and pictures activated more on the right side, and novelty scene encoding and faces symmetrically on both sides [70]. Stern [68] and Powell et al. [67] reported similar findings for word and picture encoding, but right hemispheric activation for face encoding. Other series have identified complex scene encoding to elicit slightly more right-sided mTL activation [24]. Lastly, autobiography memory retrieval demonstrated noticeable activation in the memory networks bilaterally [71].

Novelty scenes can be encoded both verbally and non-verbally; therefore, overall asymmetry may help in the lateralization of a seizure focus [14•]. In accordance with this, multiple studies have documented increased activation in the healthy Hc in mTLE patients, employing complex scene encoding and other non-verbal tasks [14•, 24, 72, 73]. It is hypothesized that this may reflect more adaptive encoding from visuospatial to verbal strategies, or vice versa, rather than any interhemispheric shifts of material-specific memory. Of note, this contralateral activation by complex scene encoding tasks was not confirmed in two subsequent series [24].

Furthermore, studies also support the concept that novelty scene encoding preferentially activates the posterior PHc and fusiform gyrus, while retrieval activates the anterior mTL, particularly the subiculum [68, 74]. Greater Hc activation for meaningful relative to meaningless stimuli and semantic relative to non-semantic tasks has also been observed [75].

Few studies have employed implicit memory paradigms, during which the subjects are not asked to remember the stimuli, so that activation of mTL structures is achieved without much cognitive effort or compliance on the part of the subject [76].

Limitations of fMRI Studies Assessing Memory

Apart from the general limitations of fMRI described elsewhere [3], hippocampal regions are small and close to bony structures; consequently, they are more susceptible to random noise, motion or measurement error [77]. The amygdala and the anterior Hc regions are also prone to lost MRI signals, due to macroscopic field inhomogeneity [14•]. Furthermore, not all the brain regions activated by memory tasks are necessarily essential for memory function, and results may be affected by some anti-seizure medications [78••]. Finally, an optimal fMRI protocol for memory testing has not yet been established, and fMRI memory paradigms differ widely between centers.

Reliability of fMRI Predicting Postoperative Memory Deficits

Richardson et al., employing an event-related design and verbal encoding task, were the first to observe that ipsilateral Hc

activation predicted verbal memory decline after left ATL better than preoperative verbal memory performance or Hc volumetry [79, 80]. Frings et al. showed that activation of the left Hc, by means of a non-verbal paradigm (object location memory task), correlated with verbal memory decline after surgery [73]. Similarly, Janszky et al. found that reduced activation of the right mTL using an imaginative walk task correlated with favorable visual memory outcomes in right ATL patients [44].

Using event-related designs and a word encoding task, Powell et al. showed that greater activation of the dominant anterior Hc, destined for resection, was linked to a higher risk of verbal memory decline. On the non-dominant side, greater ipsilateral amygdala activation for face encoding was associated with non-verbal memory decline [81]. Similarly, Bonelli et al. found that greater ipsilateral anterior Hc activation during word or face encoding predicted larger declines in verbal or visual memory after left or right ATL, respectively; while posterior Hc activation predicted better outcomes [38]. Likewise, Sidhu et al. showed that left lateralization of the frontotemporal verbal memory network was associated with verbal memory decline after left TL resection, whereas posterior Hc activation predicted better verbal memory outcomes [82•]. Wagner et al. also related greater ipsilateral functional connectivity (FC) between the Hc and superior temporal gyrus language area with verbal memory decline [74, 83] (Table 1).

WT vs. fMRI Predicting Postoperative Risk for Memory Deficits

Multiple studies have compared fMRI and WT concordance for memory lateralization in patients with TLE, with variable results.

Three small series found good correlation between the two techniques: Detre et al. found complete concordance using a complex visual scene encoding fMRI task in nine TLE patients, including two patients with paradoxical WT memory lateralization [85]. The postsurgical follow-up also showed that both techniques were useful in predicting seizure laterality [86]. Jokeit et al. found a positive correlation between fMRI activation of the left mTL during a mental way-finding task and left hemisphere WT memory performance in 18 TLE individuals [72]; Golby et al. identified concordance in 8/9 subjects using four different fMRI encoding tasks with verbal and visual stimuli [87].

However, later studies failed to confirm an acceptable level of agreement between the two tests [23]. In 2005, Deblaere et al. observed concordant lateralization between fMRI with a picture encoding task and WT with verbal and non-verbal items in ten right TLEs, but not in another eight left TLE patients [88]. Likewise, Rabin et al. reported a significantly better correlation in 20 rights than in 15 left TLE patients

Table 1 Studies evaluating fMRI usefulness for memory decline after TLE surgery

Author, year	Patient groups	fMRI paradigms and ROIs	Findings and conclusions
Richardson et al., 2004 [84]	10 L ATL	fMRI: recognition of words, some emotionally aversive. ROI: Hc	Greater activity in L Hc predicted verbal memory decline after L ATL better than neuropsychological evaluation and the Hc volume
Janszky et al., 2005 [44]	16 R ATL	fMRI: mental navigation and recall of familiar landmarks. ROI: Hc and PHC	Reduced activation of R mTL region associated with better visual memory outcome after R ATL
Richardson et al., 2006 [80]	30 L TLE (12 with ATL)	fMRI: recognition of words, some emotionally aversive. ROIs: Hc	Greater L Hc activity predicted greater postoperative verbal memory decline
Wagner et al., 2007 [83]	21 TLE (10 R, 11 L, 15 with mTL surgery)	fMRI: encoding and recognition of word pairs ROI: Hc, language BA 44–45, 22, 9–46	Greater functional connectivity between Hc and temporal language areas was associated with verbal memory decline after L and R TLE mTL surgery
Powell et al., 2008 [81]	15 ATL (8 R, 7 L)	fMRI: encoding of words, pictures and faces ROI: anterior Hc	Greater dominant-side Hc activation for words and non-dominant amygdala activation for faces was associated with greater verbal and non-verbal memory decline respectively, after ipsilateral ATL
Frings et al., 2008 [73]	22 ATL (10 R, 12 L)	fMRI: virtual encoding and recognition of object locations ROI: Hc and PHC	Ipsilateral Hc activation with a non-verbal paradigm associated with postsurgical verbal memory decline, particularly in L ATL
Bonelli et al., 2010 [4]	72 ATL (31 R, 41 L)	fMRI: encoding of words, pictures and faces ROI: anterior and posterior mTL	Asymmetrical word and face anterior Hc activation predicted verbal and visual memory decline after L and R ATL, respectively, while greater posterior Hc activation predicted better memory outcomes
Bonelli et al., 2013 [38]	46 ATL (20 R, 26 L)	fMRI: encoding of words, pictures and faces ROI: anterior and posterior mTL	Greater pre- than post-ATL activation in the L posterior mTL for word encoding linked to better verbal memory outcomes after L ATL. It is the capacity of the remnant of the Hc rather than the functional reserve of the contralateral Hc that maintains verbal memory after ATL
Sidhu et al., 2015 [82]	50 ATL (27 R, 23 L)	fMRI: encoding of words ROI: mTL, medial and inferior frontal gyri.	Left frontal and anterior mTL activations for word encoding were the best predictors of verbal memory decline after L ATL. Posterior Hc activation associated with better verbal memory outcome
Limotai et al., 2018 [24]	29 ATL (9 R, 10 L)	fMRI: novelty complex scene encoding ROI: Hc and PHC	Functional adaptations primarily occurred within the L-PHC after L ATL and within the R middle temporal gyrus after R ATL

ATL, anterior temporal lobectomy; BA, Brodmann areas; ROI, region of interest; Hc, hippocampus; L, left; mTL, mesial temporal lobe; PHC, parahippocampus; R, right; TLE, temporal lobe epilepsy

using similar fMRI and WT items. Moreover, low activation in the epileptic mTL predicted a better scene recognition outcome after ATL, whereas the WT asymmetry ratio did not [89]. Dupon et al. found low (i.e., 48%) concordance between the two techniques' lateralization indices using fMRI tasks of object encoding and immediate and delayed recognition in 14 right and 11 left TLE individuals. The sum of left mTL activation during delayed recognition, laterality of the epileptic focus, and preoperative verbal memory score, correctly predicted 90% of cases with verbal memory worsening, while WT showed no correlation with verbal or non-verbal memory

outcome. It should be mentioned that the results from this study could have been influenced by the relatively high dose of sodium amobarbital used during the WT [90••]. Kemp et al. have recently found an even lower (i.e., 31.3%) level of concordance between fMRI and WT lateralization, using the encoding of complex scenes in 12 left TLE and 4 right TLE patients [91].

Binder et al. evaluated the possibility that cortical language areas could indirectly inform about the lateralization of verbal memory. To begin, they identified good preoperative memory performance, late age at epilepsy onset, and left hemisphere

language dominance in either WT or fMRI, as predictors of postoperative verbal memory decline in 60 left ATL patients, from which language lateralization by fMRI was the second most powerful predictor (accounting for an additional 10% of the variance) [29]. Retrospectively, they showed, in another 65 right or left ATL cases, that fMRI language lateralization predicted verbal memory outcome after surgery, whereas Hc activation with a novelty scene encoding task did not (although it did correlate with WT memory lateralization) [14, 74].

Resting State fMRI (Rs-fMRI) and Memory Lateralization

rs-fMRI analyzes spontaneous activity in conditions aimed to prevent subjects from performing any cognitive task, asking participants to close their eyes and rest or, alternatively, to fixate on a cross-hair. Two types of BOLD fluctuation are observed in this situation: one related to unconstrained behavior or conscious mentation (conceptually similar to external-task paradigms); and real, spontaneous intrinsic activity. The latter reflects functional topography and can predict task-response properties of brain regions [92].

Using simultaneous EEG-fMRI techniques, Burionova et al. discovered alterations in FC within different resting state networks (RSN) in mTLE patients at rest and during the pre-spike period. These functional changes may be related to memory and other cognitive deficits seen in mTLE [93].

Among the RSNs, one deals with the default mode network (DMN), which comprises the posterior cingulate cortex (PCC), precuneus, ventromedial prefrontal cortex, inferior temporal gyri, and Hc. Interestingly, the DMN is activated during episodic or autobiographical memory retrieval and inhibited by tasks requiring external attention [23, 94]. The PCC is a key node of the DMN and its activation has been particularly implicated in successful episodic memory retrieval. Furthermore, connectivity between the PCC and mTL predicts associative memory performance in a variety of neurological disorders, like post-traumatic amnesia and Alzheimer's disease [94].

In mTLE, studies have revealed decreased connectivity between the epileptogenic or contralateral Hc and other DMN nodes, or between the anterior part of the epileptogenic Hc and the entorhinal cortex [93, 95]. A connection from the PCC to the medial prefrontal cortex has recently been found to be concomitant with left Hc inhibition in TLE patients [96].

McCormick et al. observed that both reduced connectivity from the PCC to the epileptogenic Hc and increased connectivity to the contralateral one were associated with worse presurgical memory and better postsurgical memory in both right and left mTLE patients [95]. Holmes et al. found similar results concerning verbal memory in left mTLE patients, suggesting that functional adaptive changes in the

contralateral hemisphere are inefficient at preserving verbal memory [97].

Conversely, Doucet et al. found that FC between the diseased left mTL and ipsilateral PCC was negatively correlated with verbal memory performance. At the same time, the preceding and other authors have observed that the stronger the FC is between the contralateral Hc and medial and inferior frontal cortex, the better the non-verbal memory in right TLE patients, suggesting effective of adaptive changes to preserve non-verbal memory [98, 99].

Some of these differences might be reconciled by the study methodology, as McCormick et al. [95] seeded the PCC and detected increases in FC within the Hc that might have been overlooked if the Hc was the seed.

Voets et al. showed that higher ipsilateral anterior Hc-entorhinal and lower contralateral Hc-PCC FC were associated with memory impairment. They claimed that the degree of both pathological hyper-connectivity and hypo-connectivity reflected pathological influences, rather than efficient compensatory remapping [100]. Subsequently, Li et al. found that FC between the left anterior Hc and entorhinal cortex was positively correlated with verbal memory in the left mTLE, whereas interhemispheric FC between the posterior PHc was negatively correlated with verbal memory in the right mTLE. They assumed that the strengthened FC between the bilateral posterior Hc networks compensated for the influence of the epileptogenic hemisphere on memory performance [6]. Sidhu's and Powell's studies support these results, by showing that the reorganization of the FC in the ipsilesional anterior TL effectively improved verbal memory [25, 101]. However, Li et al's findings are inconsistent with those of others, who showed that good integration of the mTLs into a posterior interhemispheric part of the DMN is associated with better episodic memory capacity [102].

Investigations depict a distinct FC pattern in the left and right mTLE, with greater FC impairment in left mTLE [6, 103]. Park et al. also recently confirmed that seizure frequency affected intratemporal FC and cognitive impairment, especially pertaining to verbal memory and language functions in left mTLE patients [22].

Cognitive Deficits in the TLE Depend on the Type of Surgical Treatment

Standard ATL may provide a better control of disabling seizures than selective amygdalohippocampectomy (SAH), whereas SAH might minimize cognitive impairment, due to the preservation of the anterior and lateral temporal neocortex [37, 104]. Supporting this, several large surgical series have demonstrated better preserved verbal and visual memory function after left and right SAH respectively, compared to ATL [49, 105].

Different cognitive sequelae have been described, depending on the type of surgery performed for left TLE. Few losses were seen after lesionectomy, whereas SAH mainly caused deficits in long-term verbal memory while improving non-memory functions, and ATL also adversely affected short-term and working memory aspects, as well as naming and semantic fluency [19, 106].

An earlier study by Katz et al. in 1989 [107] correlated greater losses in the Wechsler memory scale score with the extent of medial TL resection. Other series have suggested that a lateral extent of the ATL at less than 3 cm may prevent memory decline [19]. Joo et al. identified an association between verbal memory decline and more extensive resection of the inferior and basal temporal gyrus [108]. In contrast, other studies have discovered no difference in memory outcomes post left TLE surgery, regardless of the extent of mesial (>/< 2 cm) or lateral (>/< 4 cm) resection [109]. Wyer et al. observed no differences in memory outcomes between partial and total AH, though total AH yielded better seizure outcomes [110]. Helmstaedter et al. also found no memory change to correlate with mesial resection length (2.5 vs. 3.5 cm) or Hc remnants in patients with mesial pathology. However, when evaluated with MRI volumetry, poorer verbal memory outcome did correlate with larger resections of the left Hc, and non-verbal memory with larger resections on either side [19].

The surgical approach used in SAH also influences cognitive sequelae. The transsylvian approach may affect the superior temporal gyrus and transect the temporal stem (which connects the frontal lobe executive regions to TL language and memory areas), while the subtemporal approach may affect the basal temporal region and transect the PHc or fusiform gyrus, and transcortical approach accesses through the middle or inferior temporal gyrus [111, 112]. The results of some studies initially discouraged surgeons from pursuing the transsylvian approach, since it produced worst verbal memory decline than left temporal pole resection plus AH and worst phonemic fluency than transcortical AH [111, 113]. Non-comparative series also initially showed positive memory outcomes with a subtemporal approach. However, they did not take into consideration the effects of basal temporal lesions on language [19]. Later, the subtemporal approach demonstrated worse fluency, verbal learning, and recall than either middle or inferior transcortical [112, 113] or transsylvian SAH [111].

Ljung et al. and Gleissner et al. reported verbal memory deterioration after implanting depth electrodes along the longitudinal axis of the Hc in the dominant hemisphere or bilaterally, albeit with significant recoveries in those patients who underwent subsequent right TL resections [19, 114]. However, other studies revealed no memory deficits related to the use of intrahippocampal depth electrodes, and none have compared the cognitive effects of longitudinal versus lateral, orthogonal Hc electrodes [35].

Stereotactic laser AH might allow for higher spatial resolution and preservation of functional areas. Cognitive outcomes of stereotactic laser AH appear better than for open ATL or transcortical AH for extra-mesial functions, like naming, verbal fluency, and object and people recognition [115, 116]. However, the seizure-free rates are lower, especially in patients without MTS [117•].

Similarly, stereo-electroencephalographic (SEEG)-guided radiofrequency thermocoagulation is less effective, but considerably safer than open surgery, because of its precision and minimal invasiveness. Moreover, its effect can be used as a predictor of the outcome if subsequent resection surgery is required [118].

Stereotactic radiosurgery (i.e., gamma-knife) has high-spatial resolution and is targeted towards changing the intrinsic epileptic characteristics of radiated tissue. It is another alternative for patients with contraindications for or reluctance towards open craniotomy [119].

Finally, it is unclear if deep brain stimulation interferes with the functionality of the stimulated tissue [19]. However, multiple studies have shown efficacy and no detrimental cognitive effects when the Hc, thalamus or neocortex are stimulated [35].

Conclusions

The Hc likely provides computations for autobiographical memory, spatial navigation, and some aspects of perception and imagining. This involves integration of the individual elements and context for construction of scenes that allow for memory representations [7]. The perirhinal cortex supports encoding of the individual elements, possibly related to familiarity, whereas the posterior PHc supports encoding of spatial and temporal contexts [8, 23]. The two temporal lobes act as a bilateral system for semantic memory, in which graded hemispheric specializations emerge as a consequence of connectivity to language regions in the dominant hemisphere and, to a lesser degree, posterior visuospatial regions in the non-dominant hemisphere [5].

Adaptive recruitment within memory and extratemporal networks has been observed in mTLE patients, likely as a result of the deleterious effects of epileptic activity. In this respect, left mTLE represents a more severe form of the disease, since it is associated with more extensive FC abnormalities [98]. In such patients, the observed contralesional mTL enrollment appears insufficient to maintain memory functions. The shifting of activation to the ipsilateral TL has been observed after successful TLE surgery, but the efficiency of this adaptive reorganization for memory is not clear either [24].

The WT and fMRI are the techniques most commonly used to predict memory decline after TLE surgery. With regard to fMRI, mTL lateralization during word encoding or sentence

completion correlates better with verbal memory, whereas face or pattern recognition are better suited to lateralize non-verbal memory [4, 70]. Novelty scene or pictorial and autobiographical paradigms assess encoding and retrieval functions, respectively, and produce symmetrical bilateral activation of mTL. Therefore, mTL asymmetry detected with any of these tests is a good indicator of damage and epileptic focus lateralization [14•]. Relational processing (vs. novelty) or event-related (vs. blocked) paradigms, are more sensitive to the function of the anterior Hc and predicting memory outcomes after ATL [67, 68].

Global amnesia (or severe memory impairment) is rare after unilateral TL surgery; it has only been reported when MRI and/or neuropsychological findings indicated contralateral mTL dysfunction [31, 78]. The WT assessment for memory may result in complications and a high rate of false-positive results, which may prevent individuals from having potentially beneficial surgery. However, fMRI's ability to predict global amnesia has not been assessed, and it is not yet an alternative test to evaluate this risk. Therefore, one reasonable approach is to reserve the use of the WT for patients at higher risk of global amnesia [78]. Such a scenario occurs in two situations: patients in whom the neuropsychological evaluation shows bilateral memory problems, where WT should confirm that the contralateral Hc sustains the remaining memory; and patients with significant impairment involving "contralateral" memory, whereby the existence of functional reorganization (right Hc being responsible for verbal memory and left Hc for non-verbal memory) would be the only alternative to global amnesia.

The specificity of the WT for predicting postoperative material-specific memory decline is even more debatable, except for verbal memory decline after a left ATL in cases with a reversed asymmetry index (i.e., relatively better memory performance in the hemisphere destined for resection) [56, 60]. In any case, WT has not demonstrated any added value beyond clinical, neuropsychological, and neuroimaging data [36, 48•]. Moreover, the WT for language seems more sensitive (but less specific) for predicting memory decline than WT for memory [66]. As a result, the use of the WT has declined substantially. However, the possibility remains that the WT may contribute to predicting specific memory outcomes when neuropsychological and MRI data are inconclusive, incongruent, or infeasible [65].

On the other hand, in multiple studies that used different methods, greater fMRI activation on the left side during encoding of verbal material predicted postsurgical verbal memory decline in left mTLE [29]. Interestingly, three studies showed that fMRI memory or language lateralization was more reliable at predicting postoperative verbal memory decline than was the WT for memory or language [14•, 89, 90••].

Similarly, fMRI activation asymmetry during scene and face recognition tasks should be considered a means by which to predict non-verbal memory decline after right or left mTLE

surgery [78]. Conversely, the predictive value of WT for non-verbal memory decline has not yet been proven and its correlation with fMRI is low [91].

In summary, fMRI should be used routinely for the presurgical workup of patients with drug-resistant TLE to predict material-specific verbal and/or non-verbal memory decline. If fMRI results are ambiguous, testing can be repeated; and, only if the ambiguity is still unsolved, should WT be considered. Of note, fMRI may be less reliable in patients with large temporal lesions or an extratemporal epileptic focus [78••].

Finally, it is important to evaluate cognitive gains and losses after surgery against those that may have occurred as a natural course of TLE. Progressive memory decline in patients with mTLE has been reported, associated with lower baseline intellectual capacity, longer duration of epilepsy, increased seizure frequency, and Hc atrophy progression [21, 26]. Some studies even suggest a lifetime risk of global amnesia in patients with bitemporal pathology and poor seizure control [20]. However, not all authors have detected worsening cognitive performance over time [27].

Resting state fMRI (rs-fMRI) is a promising tool to investigate the functionality of memory networks. This task-free technique is easy to implement and can be useful in patients whose cooperation is limited because of language barriers, disability, or states of altered consciousness. Some argue that alterations in DMN connectivity may underlie the TLE-related deficits in declarative memory and contribute to others, like attention, working memory, social behavior, or language [93].

To date, rs-fMRI studies in TLE are preliminary and have yielded complex and contradictory results. However, they point out that abnormal FC between the PCC and the affected left Hc may be associated with poor episodic verbal memory performance and better postsurgical prognosis [95••, 98]. On the other hand, FC between the Hc and ipsilateral entorhinal cortex, and good integration of Hc into to the posterior inter-hemispheric part of the DMN, may contribute to better episodic memory capacity [6, 102].

Neuropsychological findings on SAH and ATL advocate for more restricted resections, though seizure outcomes may be better with larger resections. However, resection length is irrelevant if the underlying pathology is not being taken into consideration. Thus, extensive resection of an atrophied Hc will have fewer cognitive consequences than limited resection of a healthy Hc.

With regard to cognition, studies are inconsistent at discerning which surgical approach is safest for AH. The subtemporal approach affects expressive language to a greater extent, while the transsylvian approach affects phonetic fluency more than the transcortical approach [111, 113].

Stereotactic laser AH, SEEG-guided radiofrequency thermocoagulation, and stereotactic radiosurgery are relatively safe, but less effective approaches for mTLE, which may imply a lower risk of decline for naming, verbal fluency and, possibly, memory than open surgery [117•, 118, 119].

Finally, electrodes placed along the longitudinal axis of the Hc might cause memory deterioration. However, there is no evidence of adverse cognitive effects with intracranial Hc electrodes placed for neurostimulation, which appears to be an effective treatment for mTLE [35].

Compliance with Ethical Standards

Conflict of Interest A. Massot-Tarrús has received honoraria for speaking engagements and advisory boards from Bial, Eisai, and UCB Pharma, and research support from Eisai and UCB. S.M. Mirsattari is on the advisory boards and speaker bureaus for UCB Canada Inc., Eisai Limited, and Sunovion Pharmaceuticals Canada, Inc. Kevin White is an independent research consultant who was paid by Dr. Mirsattari to assist with the editing of this manuscript.

Human and Animal Rights and Informed Consent Our original study presented as part of this review paper was approved by Western University's Research Ethics Board, in London, Ontario, Canada.

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