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Review

Multiple hippocampal transections: Post-operative Memory Outcomes and Seizure Control

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ABSTRACT

Object: Temporal lobectomy with amygdalohippocampectomy is the standard surgical treatment for appropriate candidates with medically-intractable temporal lobe epilepsy. More recently, because of the risk of postoperative language/memory decline in a subset of patients with intact memory, a multiple hippocampal transection (MHT) approach has been proposed to preserve function.
Methods: Studies of MHT reporting both Engel and verbal memory outcome measures were included in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting of systematic reviews. Data were extracted on verbal memory function pre- and postoperatively, seizure outcome, and demographic factors. A random effects model was used to determine overall verbal memory function after MHT, and a meta-regression model was applied to identify factors associated with outcome.
Results: A total of 114 patients across five studies were included. Engel class I seizure outcome across all studies ranged from 64.7% to 94.7%, with 84 of the 114 patients achieving this outcome. Preoperative verbal memory score was most strongly associated with postoperative verbal memory preservation ($p = 0.003$). Of 59 patients with full verbal memory outcome scores, 86.8% (95% CI [confidence interval]: 77.6%–96%) had complete preservation of verbal memory relative to preoperative functional baseline.
Conclusion: Multiple hippocampal transection is an evolving surgical technique. Although the present data are limited, the current systematic review suggests that this approach is effective at preserving verbal memory in patients with good baseline function. Although reasonable seizure outcomes have been reported with MHT, comparison to a well-established procedure such as temporal lobectomy and amydalohippocampectomy must be guided by further evidence.

1. Introduction

Temporal lobectomy is widely accepted as the gold standard for management of temporal lobe epilepsy (TLE), the most common form of focal epilepsy in adults [1]. However, postoperative deficits in memory are a known and significant complication of hippocampectomy – especially when the underlying hippocampal architecture and neuropsychological functions are normal [2–4]. When epileptic foci are in the left temporal lobe with an anatomically normal hippocampus, there is concern for the acquisition of deficits in verbal memory following temporal lobectomy [4].

In humans, multiple hippocampal transection (MHT) was conceived following experimental data showing successful control of seizures in primates [5]. Following surgical exposure, vertical transections are made along the long axis of the hippocampus [2,3,6–10]. Hippocampal circuitry is arranged in two orthogonal planes [11]. The transverse lamellae run along the long axis of the hippocampus forming a trisynaptic loop that begins and ends in the entorhinal cortex [12]. While these pathways have been shown to play a role in memory, it is the longitudinal pathways running through the hippocampus that are primarily implicated in seizure propagation [10]. Multiple hippocampal transection aims to disrupt seizure activity while maintaining postoperative memory function through selective transection of horizontal circuits while preserving the vertically-oriented lamellae critical for memory function [13]. There have been increasing reports of this procedure preserving language and memory while also disconnecting epileptogenic circuitry and achieving postoperative seizure control [4,8,14,15]. In some series, MHT has also been combined with anterior temporal lobectomy (ATL) and/or lesionectomy with similar success in preserving function while controlling seizures [8,9].

Despite its theoretical unpinning and reports of success, MHT remains a relatively novel technique with variability in the degree of

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memory preservation reported, which limits the ability for individual patient counseling regarding the risks and benefits of surgical options. Here, we sought to systematically review the literature surrounding MHT and assess outcomes related to memory preserving and seizure control. The present work provides a review of the most up-to-date evidence on outcomes following MHT and is expected to inform future studies to guide decision-making regarding this procedure for patients with TLE.

2. Materials and methods

2.1. Study selection

The search protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary Fig. 1 for full search strategy and Supplementary Fig. 2 for PRISMA checklist). Briefly, a literature search was performed on May 10, 2019 using the keywords “multiple”, “hippocampus”, “transect”, “language”, and “temporal lobe epilepsy” in combination. The databases searched included Ovid Medline, EMbase, and PubMed with no search restrictions. All studies included patients for whom MHT was performed as an isolated procedure or as part of surgery including ATL, temporal neocorticectomy, and/or resection of lesions associated with TLE.

2.2. Data extraction and analysis

The primary outcome of interest was postoperative verbal memory, and secondary outcomes were change in verbal memory and seizure outcomes. Data were extracted from studies that reported both MHT− (pure MHT) and/or MHT+ (MHT with lesionectomy) procedures. Data abstracted included demographic information, Engel class for seizure outcome, laterality of disease and surgery, time of follow-up, and pre- and postoperative verbal memory scores on standard neurophysiological testing.

2.3. Statistical analysis

A pooled analysis was performing using R statistical software based on a random effects model. A random effects model is appropriate, as we pooled data from multiple separate studies. Each study was understood to represent a small sample of the overall population of interest.

Four studies measured verbal memory on the Wechsler Memory Scale–Third Edition (WMS-III), while Shimizu et al. [2] utilized the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). These scales have been conormalized, and no significant test-order effects were observed; therefore, we were able to compare them directly in our analysis [16]. The standard error of verbal memory outcome preservation was calculated from sample means. Heterogeneity was assessed by calculating I^2 statistic ($I^2 > 50\%$ and P value < 0.05 was considered significant). A random effects model with residual maximum likelihood estimation was used. A funnel plot was used to assess for publication bias. Meta-regression was then performed to assess covariates associated with verbal memory outcome.

3. Results

Of the 19 manuscripts identified following exclusion of duplicate search results, 13 further were excluded. The reasons for exclusions were foreign language publications (2), review articles (3), conference abstracts (4), and publications that described the same study population as two or more separate articles (4; Fig. 1; Table 1). One article, Koubeissi et al. [7], was also excluded because neuropsychological outcomes were not reported. Conference abstracts were excluded as they did not contain sufficient statistical data for inclusion in the pooled analyses presented herein. The article of Patil and Andrews [17] was excluded because the 10 patients described in the article were also described 5 years later by the same authors along with an additional 5 patients.

The remaining 5 articles underwent full-text review and consisted of original articles, written in the English language and with a unique set of patient data per article. All patients had normal hippocampal architecture on imaging, with no lesions or sclerosis. However, some patients did have lesions in the ipsilateral temporal neocortex. All the patients had medically-intractable epilepsy.

Five centers from two countries performed a total of 114 MHT surgeries between the years of 2006 and 2017. Of 114 subjects included in the studies, 59 (51.7%) had left-sided surgery and completed pre- and postsurgery formal neuropsychological evaluations for verbal memory at follow-up. Follow-up ranged from 12 to 81 months and Engel class I outcomes from 64.7% to 94.7% (Table 1). There was significant heterogeneity between studies (I^2 statistic calculation resulting in a residual heterogeneity of 79%; $p = 0.0014$; Fig. 2).

Surgical technique varied considerably between studies. Among the five studies, the following steps were universal: temporal/frontotemporal craniotomy and resection of the amygdala if there was ictal activity based on intraoperative electrocorticography or prior invasive monitoring. For the MHT, all authors fashioned steel ring transectors, and the entire thickness of the hippocampus was transected at the head, body, and tail at about 4 to 5 mm intervals. The temporal horn was accessed differently. Between 2007 and 2010, Girgis' group made an incision through the middle temporal gyrus; from 2010 onwards, they included resection of the temporal tip and temporal neocortex [9]. Usami accessed the intraventricular component via the superior temporal gyrus or a transsylvian approach [8]. Uda followed a wide sylvian split, identified the insular gyrus, and dissected along the sulcus to the ventricle [3]. Patil accessed via the middle temporal gyrus [6] and Shimizu via the anterior superior temporal gyrus [2].

The pooled frequency of verbal memory preservation was 86.8% (95% CI [confidence interval]: 77.6%–96%). This indicates that 86.8% of the patients scored at least the same as their preoperative verbal memory function after dominant temporal MHT, as measured on neurophysiological testing. Pooled neuropsychological data were calculated based on WMS-III and WAIS-III data. The pooled outcomes across 59 patients and 5 studies are presented in Fig. 3. Meta-regression analysis demonstrated that preoperative verbal memory score was strongly associated with postoperative verbal memory outcome ($p = 0.003$).

4. Discussion

Despite the risk of postoperative language and memory deficits, temporal lobectomy remains the most widely used surgical approach for TLE. Following dominant temporal lobe surgery with resection of mesial structures, verbal memory function is known to decline [9,18]. Accordingly, MHT has been reported as an approach to control seizures while preserving verbal memory function. This is accomplished by disrupting longitudinal circuitry of the hippocampus but leaving perpendicularly oriented fibers intact [2,15,19].

The present study is the first systematic review to assess the effects of MHT on postoperative verbal memory function and seizure control. In total, we identified five primary studies comprised of a total of 114 patients, 59 of whom had left-sided operations and completed pre- and postoperative verbal memory assessments. From the perspective of seizure control, MHT resulted in Engel class I outcome in 64.7–94.7% of patients.

Any comparison of MHT to temporal lobectomy with amygdalohippocampectomy should be informed by the fact that the latter has undergone the rigors of randomized controlled trials [20,21] with long-term outcomes, establishing its effectiveness. A review of 40 studies encompassing 3895 patients reported Engel class I outcome in approximately 66% of patients following anatomic temporal lobectomy [22]. Such data do not exist for MHT. The risk of postoperative memory

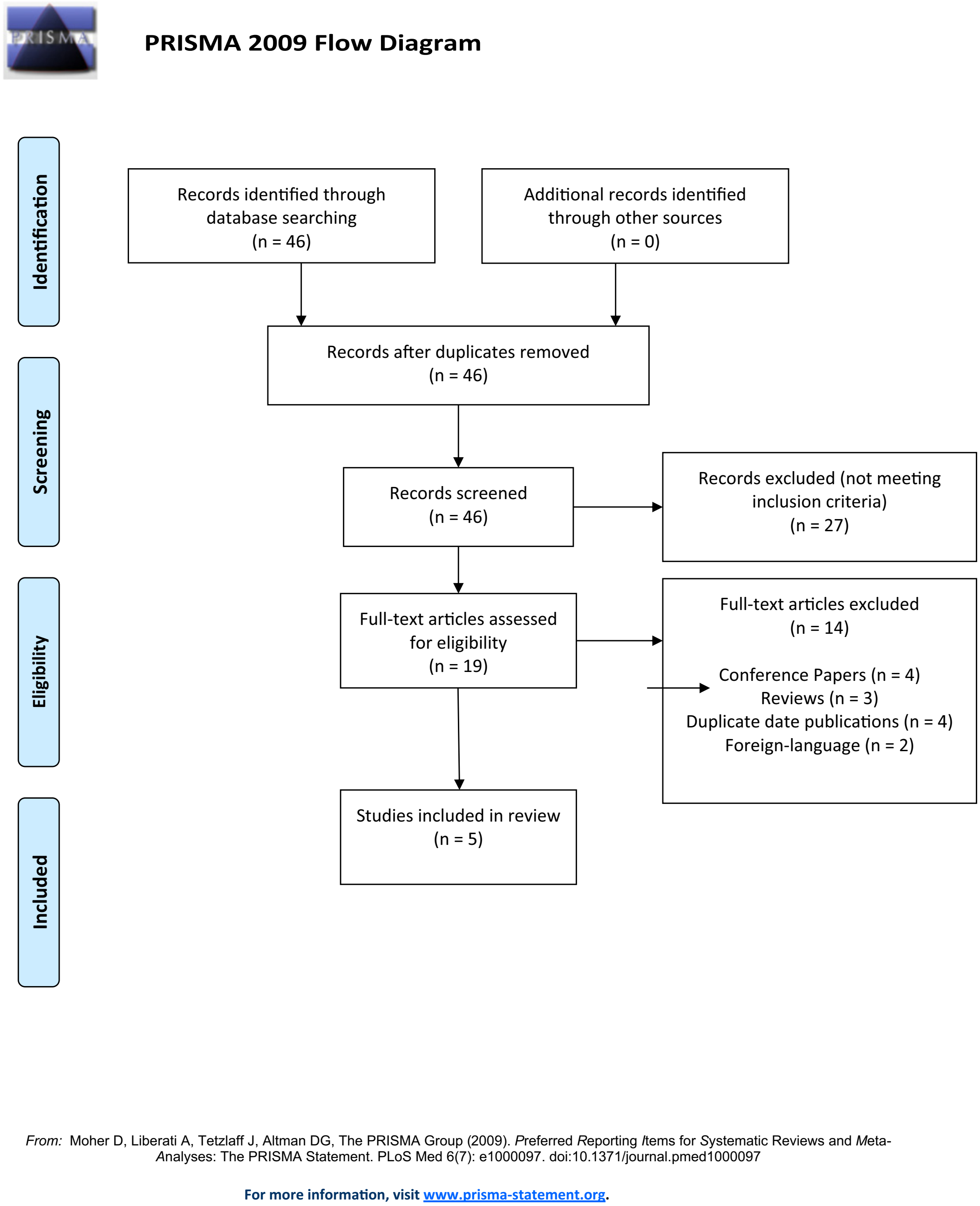

Fig. 1. PRISMA 2009 flow diagram.

decline has been well-described following resective surgery in patients with anatomically normal hippocampi [23]. While MHT may preserve verbal memory in small cohort studies, its application to individual patients needs to be balanced by limited evidence and unknown long-term effects.

Furthermore, the concept of MHT was based upon multiple subpial transections, which showed early promise in managing seizures arising from eloquent neocortical regions [2,24]. Indeed, longer-term follow-up of these patients has revealed that up to 50% of patients experience significant seizure recurrence [24]. Two hypotheses have surfaced to

Table 1
Study demographics. Overview of the included studies, including percent of patients attaining Engel class I, III, and III outcomes (E1, EII, and EIII, respectively). Laterality, number of patients with neuropsychological testing, as well as pre- and postoperative verbal memory outcomes are reported.

Authors	Year	Country	N	FU	EI%	EII%	EIII %	Left-sided MHT	Right-sided MHT	Patients with verbal memory outcome	Preop verbal memory	Postop verbal memory
Girgis	2017	USA	17	12	64.7	29.4	5.9	15	2	14	95.2 ± 3.3	94.1 ± 25.1
Usami	2016	Japan	24	81	71	25	4	16	8	12	85 ± 3.8	78 ± 5.2
Uda	2013	Japan	37	49	67.6	27	5.4	18	19	18	91.5 ± 4.3	87.7 ± 5.2
Patil	2013	USA	15	40.7	94.7	5.3	0	11	4	8	66.3 ± 4.5	75.6 ± 2.9
Shimizu	2006	Japan	21	12	82.4	12	6	12	9	7	95.7 ± 6.5	100 ± 6.2

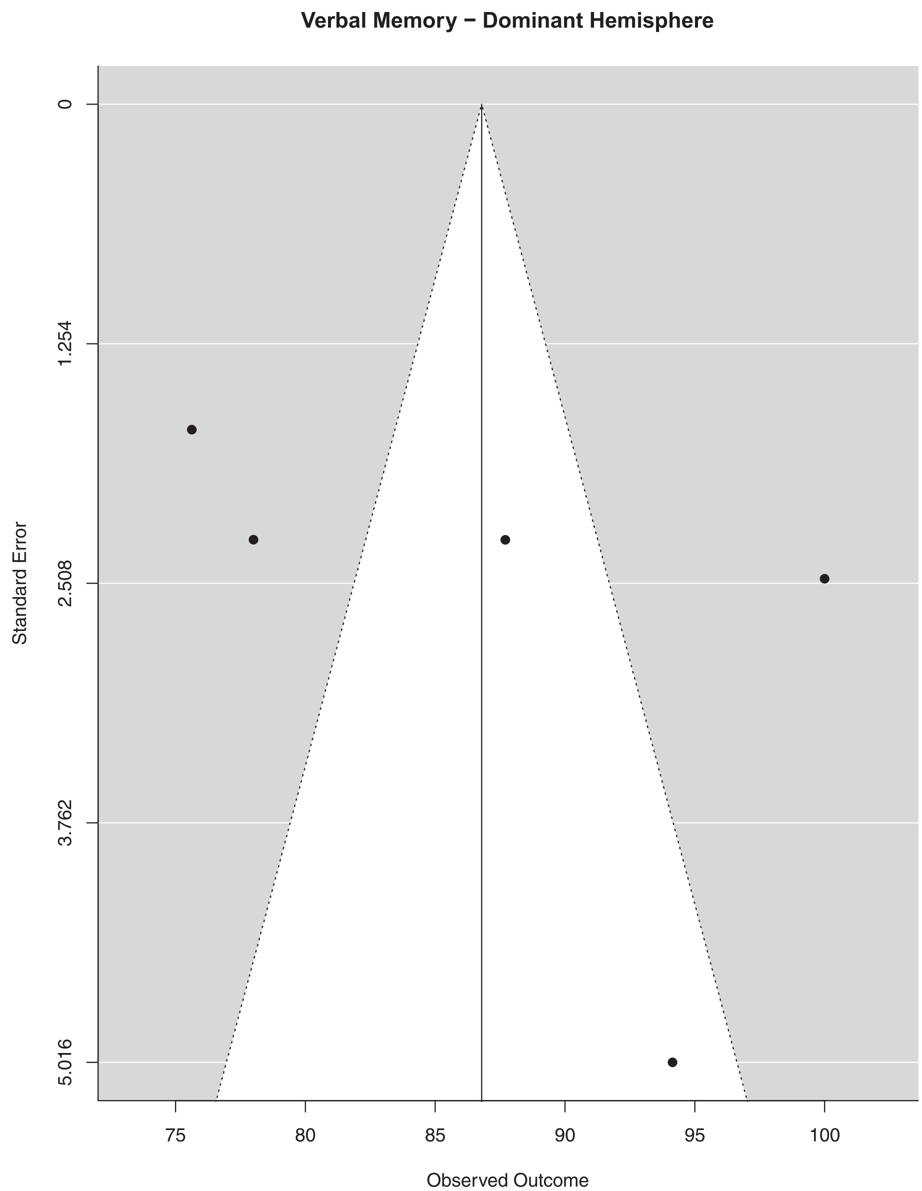

Fig. 2. Funnel plot.

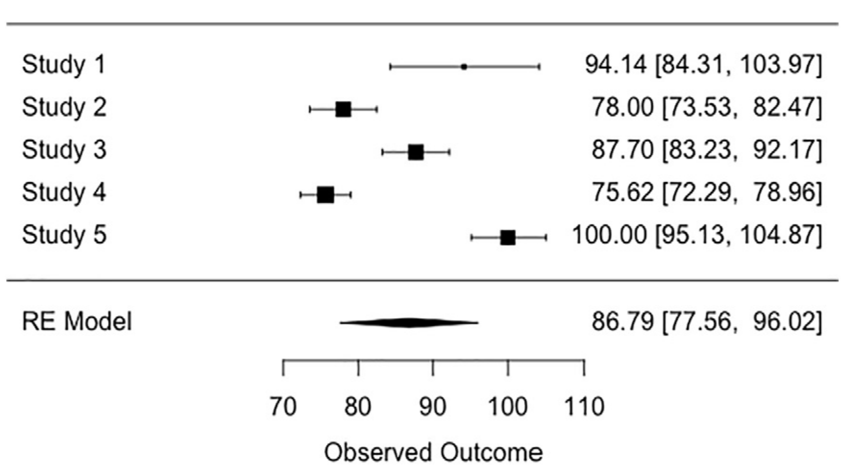

Fig. 3. Verbal memory outcome following MHT surgery. Squares represent each independent study. The diamond shows pooled data with 95% confidence intervals.

explain this finding: postoperative cortical injury and gliosis leading to new epileptogenic foci or the recruitment of alternate epileptogenic circuitry over time [24]. In our study, the only long-term follow-up was in the Usami study [8]. Further study is therefore needed to clarify the risk of seizure recurrence following MHT.

As one might expect, a higher preoperative verbal memory score was associated with better postoperative verbal function ($p = 0.003$). This again points toward the role of MHT in patients with functionally normal hippocampi. Conversely, the effect of MHT for sclerotic hippocampi is less clear. Here, the underlying neuronal architecture is abnormal and may not follow the orthogonal orientations required for successful MHT. Furthermore, the neuropsychological literature has increasingly pointed toward improvements in contralateral (visuospatial) memory function following resective surgery in the dominant temporal lobe [25]. This evidence, though limited, suggests that these patients are better served by resective surgery, especially when preoperative memory function is already compromised [8]. Of note, in our review, MHT did lead to improvement in verbal memory in a small subset of patients with poor preoperative verbal memory function. Unfortunately, this population is too small within our series to draw specific conclusions, and the mechanisms of this effect remain a topic of uncertainty and future inquiry.

Our work is limited by the available data. The high degree of heterogeneity reflects the small number of studies and patients included as well as a lack of standardization between studies. For example, surgical technique varied considerably between – and even within – studies. Though the core steps to performing the MHT were similar, the temporal horn was accessed differently with varying degrees of temporal neocortical resection. Although this variability is common within surgical series, it limits the conclusions of our findings. Dates and lengths of follow-up were also not standardized and varied significantly between each study. These discrepancies, as well differences in the patient populations themselves, are likely significant contributors to the heterogeneity we have seen. A final limitation is the lack of control populations. Future studies directly comparing MHT with standard temporal lobectomy and amydalohippocampectomy may not be feasible, however, given that patients at high risk of postoperative memory deficit are not typically offered the latter.

5. Conclusions

Multiple hippocampal transection is increasingly described in cases of mesial TLE with the aim of preserving postoperative memory function. This technique aims to take advantage of orthogonal circuitry in the hippocampus by selectively disconnecting epileptogenic circuits while maintaining those responsible for memory function. Multiple hippocampal transection appears to offer promising rates of Engel class I seizure control; however, the durability of this effect over long time periods still requires further study based on disappointing results obtained with multiple subpial transections for neocortical epilepsy. Subject to further investigation, MHT may serve as a useful technique for patients with mesial TLE in whom memory preservation is a significant concern, but direct comparison to amgdalohippocampectomy is not yet possible given the wealth of evidence supporting the latter.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106496.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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