Stereotact Funct Neurosurg 2013;91:134–137
DOI: [10.1159/000348268](https://doi.org/10.1159/000348268)

Caveat Emptor: Bitemporal Intractable Epilepsy: Could It Be Surgically Treated?

Robert E. Gross^{a-c}, Daniel L. Drane^b,

Departments of ^aNeurosurgery and ^bNeurology, Emory University, and ^cCoulter Department of Biomedical Engineering, Emory University and Georgia Tech, Atlanta, Ga., USA

For patients with bilateral temporal lobe epilepsy, present-day surgical approaches offer little hope for seizure freedom. Given a fairly large number of patients with this problem (~30% of patients with medically refractory temporal lobe epilepsy), new approaches are urgently needed, especially considering that patients with bitemporal onsets may have higher seizure rates and experience greater neurocognitive deficits than unilateral temporal lobe epilepsy patients. Two recent clinical trials of nonablative electrical neuromodulation approaches (deep brain stimulation of the anterior thalamic nucleus [1], responsive neurostimulation trial [2]) hold promise, but (a) the seizure-free rate in both trials was only around 10% overall (the numbers for hippocampal patients per se have yet to be reported), and (b) neither approach has been approved as yet by the US FDA, although thalamic stimulation is approved in Canada and Europe.

If no new approach is very promising, then what about an *old* approach? In this issue, Chkhenkeli et al. [3] report the results of *bilateral* stereotactic, restricted cryoablation (an ‘old’ technique) of the amygdala and hippocampus in the treatment of patients with bilateral mesial temporal lobe epilepsy. This approach achieved seizure freedom in 52% and rare seizures in 29% of patients at long-term (mostly) follow-up. Perhaps more notably, there was – they argue – seemingly minimal impact on memory in most patients, with no patient manifesting the dreaded ‘grave’ effects on recent memory described by Scoville and Milner [4] following the former’s bilateral mesial temporal resections. If true, the implications of this approach would be substantial, especially considering the advent of *new* ways to perform limited, controlled stereotactic ablations.

As noted by Chkhenkeli et al. [3], bilateral temporal lobe surgery is considered *taboo*: nary a neuroscience student is unaware of the late H.M. (even if they can’t tell you his name: Henry Molaison), the single most tested individual in the history of mankind [5]. Following the experimental ‘radical’ bilateral mesial temporal

lobe suction ablation performed by William Scoville in Hartford in 1953 to treat his epilepsy, H.M. apparently never encoded another declarative memory (although procedural memory remained strikingly intact) [5]. As related by Milner, after decades of testing him, MIT’s Suzanne Corkin asked H.M. if he recognized her, to which he responded: ‘Did we go to high school together?’ (an indication that familiarity is a distinct nonhippocampal process [6]). This case gave striking support to the deduction drawn by Penfield and Milner [7] that bilateral hippocampal damage results in catastrophic loss of anterograde memory, based on 2 amnesic cases of their own in which they surmised bilateral hippocampal injury. In fact, 2 other patients of Scoville and Milner [4] who received similar bilateral resections for psychiatric disorders had exactly the same pattern of memory loss. Bilateral surgery has been shunned ever since. In fact, it was to avoid inadvertently inflicting profound amnesia that Milner et al. [8] refined Wada’s sodium amytal procedure for memory testing.

Chkhenkeli et al. [3] point out, however, that the landmark cases described above involve large temporal resections (8 cm from the temporal tip) encompassing most/all of the amygdala, uncus, hippocampus, and parahippocampal gyrus (including entorhinal cortex), back to the level of the tectal plate, ‘not comparable with precise and controllable stereotactic lesions’. This may be true, as a justification for the latter, but they overstate the case by embarking on discussion of the cases of human ‘Klüver-Bucy syndrome’ [9], which incorporated basal and lateral temporal gyri within the resections, in contrast to Scoville’s surgery. In fact, MRI [10] analysis of H.M.’s brain showed that the resection was more limited than reported by Scoville and Milner [4], preserving ~2 cm of the posterior hippocampus, which – although somewhat atrophic – represents ~50% of its intraventricular extent. Additionally, perirhinal cortex (around the collateral sulcus) and fusiform gyrus are relatively preserved. Thus, the resection was not as radical as thought, i.e. ~5 cm rather than 8 cm from the temporal tip, and more consistent with one other of Scoville’s patients that became amnesic with a 5-cm resection, and also one of the patients of Penfield and Mathieson [11] that had a similar size resection based on autopsy. These facts are important because they implicate bilateral resection of more anterior structures in the etiology of amnesia, including the hippocampal head/anterior body and the entorhinal cortex.

Thus, Chkhenkeli et al. [3] hypothesized that *bilateral subtotal stereotactic ablations* of the amygdala (amygdalotomy) and/or hippocampus (hippocampotomy) – sparing parahippocampal gyrus and other regions, and limited to ictogenic regions – would be effective in treating seizures and preserve anterograde memo-

ry. This is not entirely unfounded: in the monograph by Scoville and Milner [4] are reported 5 patients who underwent smaller resections as per Scoville (4–5 cm from the temporal tip) and who had moderate but not catastrophic memory decline. If Scoville's '8 cm resection' spared 50% of hippocampus, one wonders whether the '4–5 cm' version spares more, perhaps 75%, i.e. just a resection of the hippocampal head. Moreover, bilateral amygdalotomy has also been shown by Scoville to preserve memory. Twenty-one patients were operated on, from 1980–1995, in Tbilisi, the capital of the republic of Georgia, using the classical but resurgent technique of stereoencephalography (SEEG) pioneered by Talairach and Bancaud at St. Anne Hospital in Paris. Defining interictal and ictal onset zones with depth electrodes, Chkhenkeli et al. [3] then performed cryoablation of the amygdala and/or hippocampus, plus other 'limbic' structures such as the anterior cingulate (area 24), dorsomedial thalamus, and centromedian nucleus in various combinations. The specific ablations performed are listed in their table 1, and summarized as follows:

- (1) Five patients, who developed contralateral onsets following previous anterior temporal lobectomy and 'nearly complete hippocampectomy', underwent contralateral, subtotal stereotactic cryoamygdalotomy and partial anterior cryohippocampotomy' (uncal segment, pes and digitations).
- (2) Sixteen de novo patients underwent the following stereotactic cryoablations:
 - (a) on the side of dominant epileptic focal activity, 'total' hippocampotomy, plus 'total amygdalotomy',
 - (b) on the contralateral side, partial anterior (as above) hippocampotomy and 'limited amygdalotomy' of the basal, lateral and central nuclei (to preserve input to the ventromedial hypothalamus).
- (3) Additionally, bilateral anterior cingulotomies were performed in 5, dorsomedial thalamotomies in 2 and centromedian thalamotomies in 5.

Unfortunately, although the authors state that 'the epileptic focus activity recorded by each SEEG... determined the volume of the lesion', it is not made clear how. They do not present the results of the SEEG (except in 1 case) so that we can see how the ablations related to the electrophysiology. A 'total' hippocampotomy was always done on the side of dominant epileptic activity: was the entire hippocampus always involved on that side? A 'partial anterior' hippocampotomy was always done on the side contralateral to the dominant epileptic activity: was epileptic activity always restricted to the anterior hippocampus on that side? Since this is unlikely, what were the implications of not ablating posterior areas that may have been active? Obviously, this is *critical* information, since the whole premise here is that 'volume-controlled ablation of abnormally discharging hippocampal tissue' will be effective, and safe with respect to memory. Moreover, no postlesion imaging was presented to demonstrate the true extent of the lesions.

Irrespective of the heterogeneity and ambiguity, a few salient points can be gleaned. First, a reasonable percentage of patients with bilateral mesial temporal lobe epilepsy could be made seizure-free (52%) following a unilateral 'total amygdalohippocampotomy' plus a contralateral partial amygdalotomy and partial anterior hippocampotomy (ostensibly confined to the area with seizure onset). The implications of this are twofold:

- (1) *Hippocampotomy alone*, i.e. sparing the parahippocampal gyrus (including entorhinal cortex), is sufficient for stopping mesial temporal lobe seizures. In fact, this finding is a replication of Malikova et al. [12], who in a post hoc analysis of their series of stereotactic radiofrequency hippocampotomies showed that ablation of the entorhinal and perirhinal cortices did not influence seizure-free outcome. We have also observed this in our series of patients following stereotactic MRI-guided laser thermal hippocampotomies confined to the amygdala and hippocampus proper (personal observations), where thus far 3 of 6 patients with mesial temporal sclerosis are seizure-free after 6–16 months. Conversely, 2 patients underwent parahippocampal gyrus ablations that incompletely involved the hippocampus and neither became seizure-free. It may well be that ablation of the hippocampus is necessary and sufficient to stop mesial temporal lobe seizures, a finding that – despite many thousands of mesial temporal lobe resections having been performed – has never been examined because invariably the parahippocampal gyrus is incorporated therein.
- (2) *Anterior hippocampotomy* is also sufficient. The caveat here is that, in addition to lack of MRI verification, the authors are unclear about the relationship of SEEG recordings to the limited lesions. If the onsets were posterior, was the contralateral posterior hippocampus spared? How often did this happen and did those patients continue to have seizures? If the onsets were posterior, then why did they not lesion that area in some patients? Nevertheless, there is a literature on anterior hippocampotomy. Although seizure freedom likely correlates – to a point – with extent of hippocampal resection along the longitudinal axis, Wyler et al. [13] and Schramm et al. [14] amongst others showed that anterior limited resection is effective in a subset of patients.

Conceding, caveat emptor, that bilateral amygdalohippocampotomy as performed by Chkhenkeli et al. [3] was reasonably effective for bilateral mesial temporal lobe epilepsy, have they convincingly shown that it 'will not cause additional memory and learning decline'? We feel that difficulties in interpreting the available cognitive data as well as clear inadequacies in assessment of hippocampal function make this conclusion suspect for the following reasons:

- (1) The authors did not use standardized measures of declarative memory function whose sensitivity and specificity to detect mesial temporal mediated memory processes have been validated, because 'it was impossible to establish the preoperative memory baseline and score it'. This justification will not sway most present-day neuropsychologists whose tools do just that in patients with temporal lobe-based memory decline [15, 16]. Rather, the single memory measure used by the authors reflects a nonvalidated, novel method, which has not been established to be sensitive to damage to the hippocampus, lacks normative data for either epilepsy patients or healthy controls, and does not appear to thoroughly assess memory and learning as structured (the lack of detail regarding the unorthodox memory procedure makes it difficult to interpret altogether). Chkhenkeli et al. [3] appear to have given the same tests, one attempting to assess visual memory and the other verbal, 3 times both pre- and postsurgically, and then took the average of the 3 recall performances to get what they are referring to as 'reliable memory scores'. The potential range of scores is only

0–10 on either their verbal or visual memory tasks, with very little variance within or across patients (i.e., average scores on both tests ranged from 6 to 8 out of a possible 10 points, and movement from pre- to postsurgical performance was typically less than a half point (see their table 1). Overall, it is quite possible that these measures reflect insensitive tools with highly restricted performance ranges. In particular, assessment of hippocampal function should involve an assessment of ‘relational’ memory (e.g., pairing words together or to other sensory stimuli) rather than only ‘item’ memory as assessed in the current study. Item memory has been shown to be far less impacted by lesions restricted to the hippocampus than is relational memory [17, 18]. Even in our small series of patients undergoing unilateral laser ablation, most are experiencing some degree of episodic memory decline despite seemingly preserved or even improved outcome for naming and object recognition.

(2) Other psychometric concerns include:

- (a) They used a recall time span of only 5 min, which may not have been adequate to truly assess memory consolidation, retention, and retrieval.
- (b) Although they do not describe the format of their tests, it is clear that some tasks had to have used a recognition recall paradigm (e.g., recalling unfamiliar faces could not have been completed any other way). Recognition recall can be successfully performed by patients with hippocampal damage, as this process can be performed on the basis of ‘sense of familiarity’, a process that does not appear to be mediated by the hippocampus [6].
- (c) None of their work considers the impact of practice effects nor is there likely any way to calculate such effects from their available data.
- (3) All patients included in this study had a relatively early age of seizure onset (range = 3–15 years). Numerous studies have demonstrated that epilepsy patients with early seizure onset are more likely to have undergone reorganization of function [19], so it is possible that memory and other cognitive functions are represented in an atypical manner in many of these patients. Therefore, these findings may not apply to older onset patients who would be less likely to have undergone reorganization.
- (4) Chkhenkeli et al. [3] note that they tested some patients at multiple postsurgical time points, but indicate that they sometimes relied on self-report or family report to determine if change had occurred. Once again, multiple studies have demonstrated that both self-report and the report of others can be misleading in establishing the presence or absence of cognitive or mood dysfunction, as deficits are often not fully appreciated or accurately described. We have had patients unable to name their family members who did not self-disclose these deficits when asked to summarize postsurgical change.

Overall, multiple factors are present in the present study design that would likely bias the results in favor of not finding deficits even with proper assessment measures, and the sole memory tools used by Chkhenkeli et al. [3] are unlikely to be adequately assessing learning and memory. So, why publish this report if the neuropsychological assessments were inadequate to address the hypothesis that bilateral hippocampal ablation can be performed without adversely affecting memory performance? This is a provocative idea, one meritorious of further research, and one with potential large impact for patients with bitemporal seizure onsets who are seeking

seizure freedom. There are no other alternative treatments available at this time, with the fate of the responsive neurostimulation trial (Neuropace) hanging in the balance at the USFDA. Chkhenkeli et al. [3] can be congratulated for thinking outside the box, all the more considering – or perhaps as a result of – the time and location of these surgeries. Nevertheless, extreme caution should be exercised in accepting the interpretation of these results and their implications.

Nevertheless, the findings of Chkhenkeli et al. [3] do have precedent – in the very report that generated the taboo of performing bilateral mesial temporal lobe resections. Scoville and Milner [4] reported that 5 patients who underwent bilateral mesial resections experienced only ‘moderate memory defects’ (based on Wechsler Memory Quotient as well as qualitative evaluations), rather than the ‘grave’ amnesia that characterized H.M. and 2 others (and Milner is a neuropsychologist of not insignificant repute). Scoville estimated that these patients had 4.5- to 6-cm resections (from temporal tip), less than the 8-cm resections of 2 of the amnesic patients. Although the third amnesic patient had a 5.5-cm resection, as shown by Corkin et al. [10] that estimation is not completely reliable. The implication of Scoville and Milner [4] is that in fact bilateral surgery is not catastrophic, as we have been inclined to think ever since. However, whether it is as benign as implied by the present report, perhaps due to confining the lesions to the hippocampus proper, or leads to a ‘moderate defect’ as in the classic paper, remains to be determined by future studies with more careful delineation of the lesions created as well as the neurocognitive impacts they create.

References

- 1 Fisher R, Salanova V, Witt T, et al: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010; 51:899–908.
- 2 Morrell MJ; Group RSIES: Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.
- 3 Chkhenkeli SA, Šramka M, Rakviashvili TN, Lortkipanidze GS, Magalashvili GE, Bregvadze ES, Otashvili A, Gagoshidze TS: Bitemporal intractable epilepsy: could it be surgically treatable? *Stereotact Funct Neurosurg* 2013;91:104–112.
- 4 Scoville WB, Milner B: Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 1957;20:11–21.
- 5 Corkin S: What’s new with the amnesic patient H.M.? *Nat Rev Neurosci* 2002;3:153–160.
- 6 Eichenbaum H, Yonelinas AP, Ranganath C: The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123–152.
- 7 Penfield W, Milner B: Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch Neurol Psychiatry* 1958;79:475–497.
- 8 Milner B, Branch C, Rasmussen T: Study of short-term memory after intracarotid injection of sodium amytal. *Trans Am Neurol Assoc* 1962; 87:224–226.
- 9 Terzian H, Ore GD: Syndrome of Klüver and Bucy; reproduced in man by bilateral removal of the temporal lobes. *Neurology* 1955;5:373–380.
- 10 Corkin S, Amaral DG, González RG, Johnson KA, Hyman BT: H.M.’s medial temporal lobe lesion: findings from magnetic resonance imaging. *J Neurosci* 1997;17:3964–3979.
- 11 Penfield W, Mathieson G: Memory: autopsy findings and comments on the role of hippocampus in experiential recall. *Arch Neurol* 1974;31:145–154.
- 12 Malikova H, Liscak R, Vojtech Z, et al: Stereotactic radiofrequency amygdalohippocampectomy: does reduction of entorhinal and perirhinal cortices influence good clinical seizure outcome? *Epilepsia* 2011;52:932–940.

- 13 Wyler AR, Hermann BP, Somes G: Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery* 1995;37:982–990; discussion 990–981.
- 14 Schramm J, Lehmann TN, Zentner J, et al: Randomized controlled trial of 2.5-cm versus 3.5-cm mesial temporal resection – part 2: volumetric resection extent and subgroup analyses. *Acta Neurochir (Wien)* 2010; 153:221–228.
- 15 Loring DW, Hermann BP, Meador KJ, et al: Amnesia after unilateral temporal lobectomy: a case report. *Epilepsia* 1994;35:757–763.
- 16 Loring DW, Lowenstein DH, Barbaro NM, et al: Common data elements in epilepsy research: development and implementation of the NINDS epilepsy CDE project. *Epilepsia* 2011;52:1186–1191.
- 17 Konkel A, Warren DE, Duff MC, Tranel DN, Cohen NJ: Hippocampal amnesia impairs all manner of relational memory. *Front Hum Neurosci* 2008;2:15.
- 18 Verfaellie M, LaRocque KF, Keane MM: Intact implicit verbal relational memory in medial temporal lobe amnesia. *Neuropsychologia* 2012;50: 2100–2106.
- 19 Saykin AJ, Gur RC, Sussman NM, O'Connor MJ, Gur RE: Memory deficits before and after temporal lobectomy: effect of laterality and age of onset. *Brain Cogn* 1989;9:191–200.