

Extrapial Hippocampal Resection in Anterior Temporal Lobectomy: Technical Description and Clinical Outcomes in a 62-Patient Case Series

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BACKGROUND: Anterior temporal lobectomy (ATL) is the most effective treatment for drug-resistant mesial temporal lobe epilepsy. Extrapial en bloc hippocampal resection facilitates complete removal of the hippocampus. With increasing use of minimally invasive treatments, considering open resection techniques that optimize the integrity of tissue specimens is important both for obtaining the correct histopathological diagnosis and for further study.

OBJECTIVE: To describe the operative strategy and clinical outcomes associated with an extrapial approach to hippocampal resection during ATL.

METHODS: A database of epilepsy surgeries performed by a single surgeon between October 2011 and February 2019 was reviewed to identify all patients who underwent ATL using an extrapial approach to hippocampal resection. To reduce confounding variables for outcome analysis, subjects with prior resections, tumors, and cavernous malformations were excluded. Seizure outcomes were classified using the Engel scale.

RESULTS: The surgical technique is described and illustrated with intraoperative images. A total of 62 patients met inclusion criteria (31 females) for outcome analysis. Patients with most recent follow-up <3 yr (n = 33) and >3 yr (n = 29) exhibited 79% and 52% class I outcomes, respectively. An infarct was observed on postoperative magnetic resonance imaging in 3 patients (1 asymptomatic and 2 temporarily symptomatic). An en bloc specimen in which the subiculum and all hippocampal subfields were preserved was obtained in each case. Examples of innovative research opportunities resulting from this approach are presented.

CONCLUSION: Extrapial resection of the hippocampus can be performed safely with seizure freedom and complication rates at least as good as those reported with the use of subpial techniques.

KEY WORDS: Epilepsy, Mesial temporal lobe, Hippocampus, Temporal lobectomy, Ambient cistern

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Epilepsy is one of the most serious neurological disorders worldwide,¹ affecting 1% of the world's population and drug resistant in at least 30% of cases.² Temporal lobe epilepsy (TLE) is often surgically remediable, with 2 randomized control trials^{3,4} demonstrating the superiority of anterior temporal

lobectomy (ATL) over medical treatment, but epilepsy surgery remains underutilized.^{5–7} Strategies to improve therapeutic options include advancing new clinical approaches, such as minimally invasive laser interstitial thermal therapy⁸ and responsive neurostimulation,⁹ and advancing the basic science of epilepsy by optimizing the opportunity to study resected tissue. With reduced numbers of ATL surgeries due to increasing use of minimally invasive options,^{6,10} however, there is a growing inability to collect intact hippocampal specimens from patients with epilepsy.

The classic technical approach to ATL preserves the mesial pia and avoids opening

ABBREVIATIONS: ATL, anterior temporal lobectomy; CA, cornu Ammonis; PCA, posterior cerebral artery; STG, superior temporal gyrus; TLE, temporal lobe epilepsy

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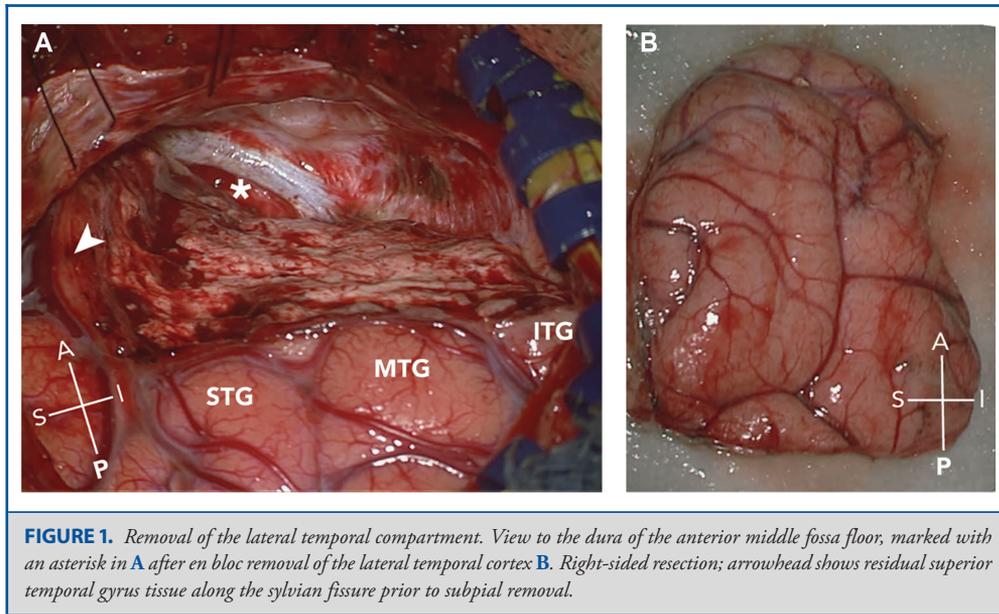


FIGURE 1. Removal of the lateral temporal compartment. View to the dura of the anterior middle fossa floor, marked with an asterisk in **A** after en bloc removal of the lateral temporal cortex **B**. Right-sided resection; arrowhead shows residual superior temporal gyrus tissue along the Sylvian fissure prior to subpial removal.

the cisternal space when resecting the hippocampus.¹¹⁻¹⁴ Here, we report the use of a different strategy that evolved early in a single-surgeon practice as a means to optimize anatomic precision for complete resection of the hippocampus. In this variation of the standard ATL, an extrapial approach via opening of the crural and ambient cisterns using microvascular techniques safely facilitates optimal isolation of the hippocampus. Given that incomplete resection of the hippocampus has been associated with less chance for seizure freedom,¹⁵ this technique may facilitate optimal seizure outcomes. Secondarily, structural preservation of the hippocampus achieved by this approach has been found to enable novel microscopic and mesoscopic ex vivo explorations in epilepsy neuroscience.

METHODS

Subjects

A prospective database was used to perform a retrospective cohort review of a consecutive case series of all epilepsy surgeries performed between October 2011 and February 2019 (Research Registry UIN 6247). The database and informed consent were approved by the Institutional Review Board, and all subjects gave informed consent. Inclusion criteria were the following: diagnosis of drug-resistant TLE and planned removal of the hippocampus by an extrapial approach, as indicated in the operative report. Exclusion criteria were the following: previous temporal lobe surgery, additional extratemporal seizure foci, or presence of a tumor or cavernous malformation. Recommendations for surgery were made by an interdisciplinary team according to established international league against epilepsy criteria¹⁶ and postoperative magnetic resonance imaging (MRI) was obtained within 14 d of surgery.

Statistics

Pearson χ^2 test and unpaired *t*-tests were used for univariate analysis of independent variables. Logistic multiple regression analysis was used to model all independent variables together and adjust for potential confounders. The primary endpoints for all tests were whether seizure freedom (Engel class I)¹⁷ or favorable seizure control (combined Engel class I and II) was achieved at 40 mo and whether a postoperative complication occurred. A last observation carried forward methodology was used for all statistical tests, including Kaplan-Meier curves. All tests were 2-sided, and an a priori threshold for significance of 0.05 was used.

RESULTS

Surgical Technique

The strategy for extrapial resection of the hippocampus is an extension of thinking about the ATL procedure as one of anatomical compartmentalization of each step. Understanding anatomical landmarks and relationships in the temporal lobe facilitates en bloc resection of each compartment.

The first anatomic compartment removed is the lateral temporal cortex. On the language dominant side, when maximal resection of lateral cortex is desired based on the hypothesized seizure onset zone, awake mapping with direct cortical stimulation determines the posterior boundary of the resection on the superior, middle, and inferior temporal gyri. The intended volume of lateral cortex is resected en bloc to the level of the temporal stem medially. The bed is rotated toward the operating room floor to visualize the anterior-most aspect of the middle fossa (Figure 1). Inferiorly, the pia is cut along the inferior temporal gyrus to the temporal pole, to facilitate en bloc removal.

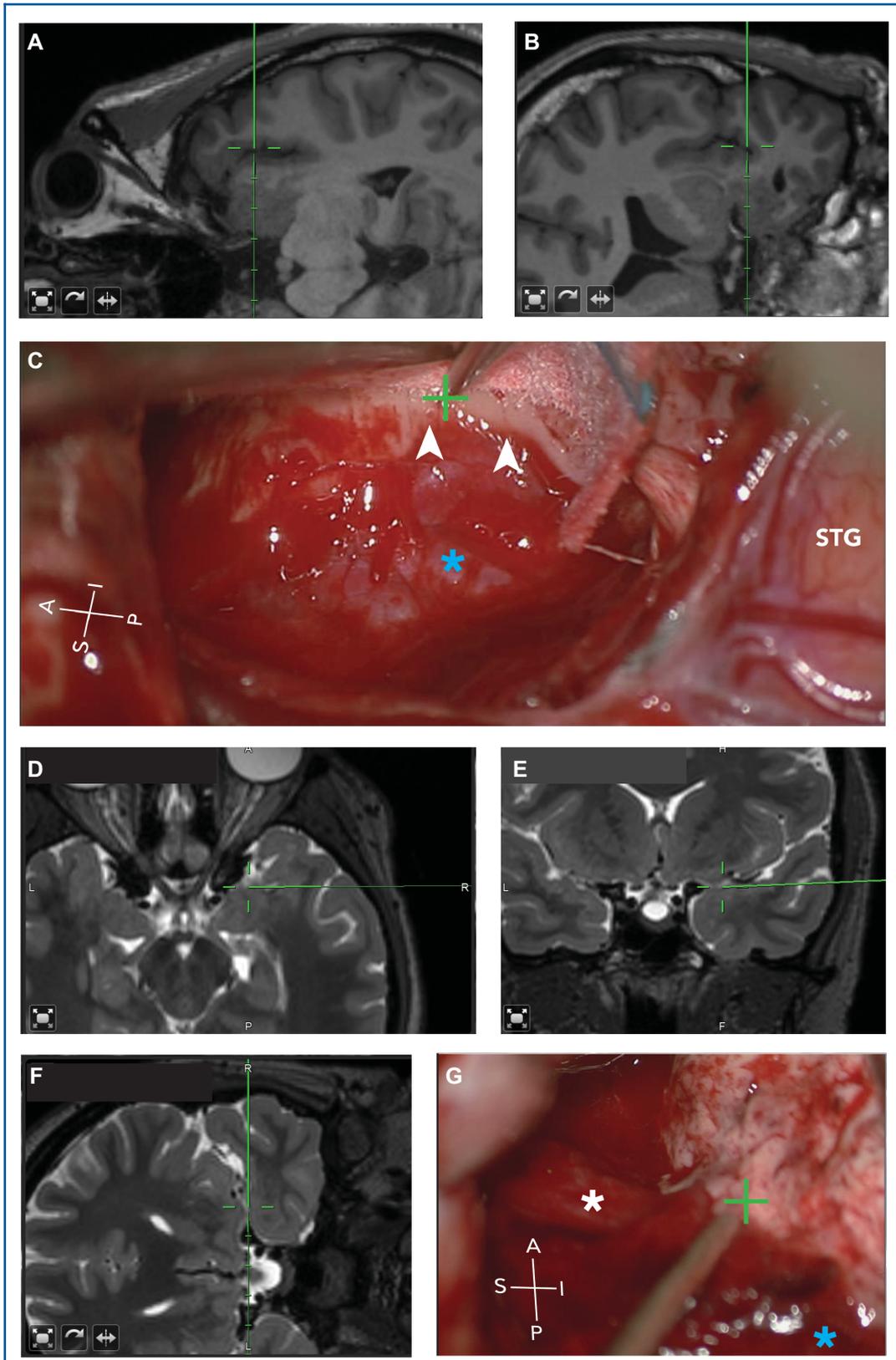
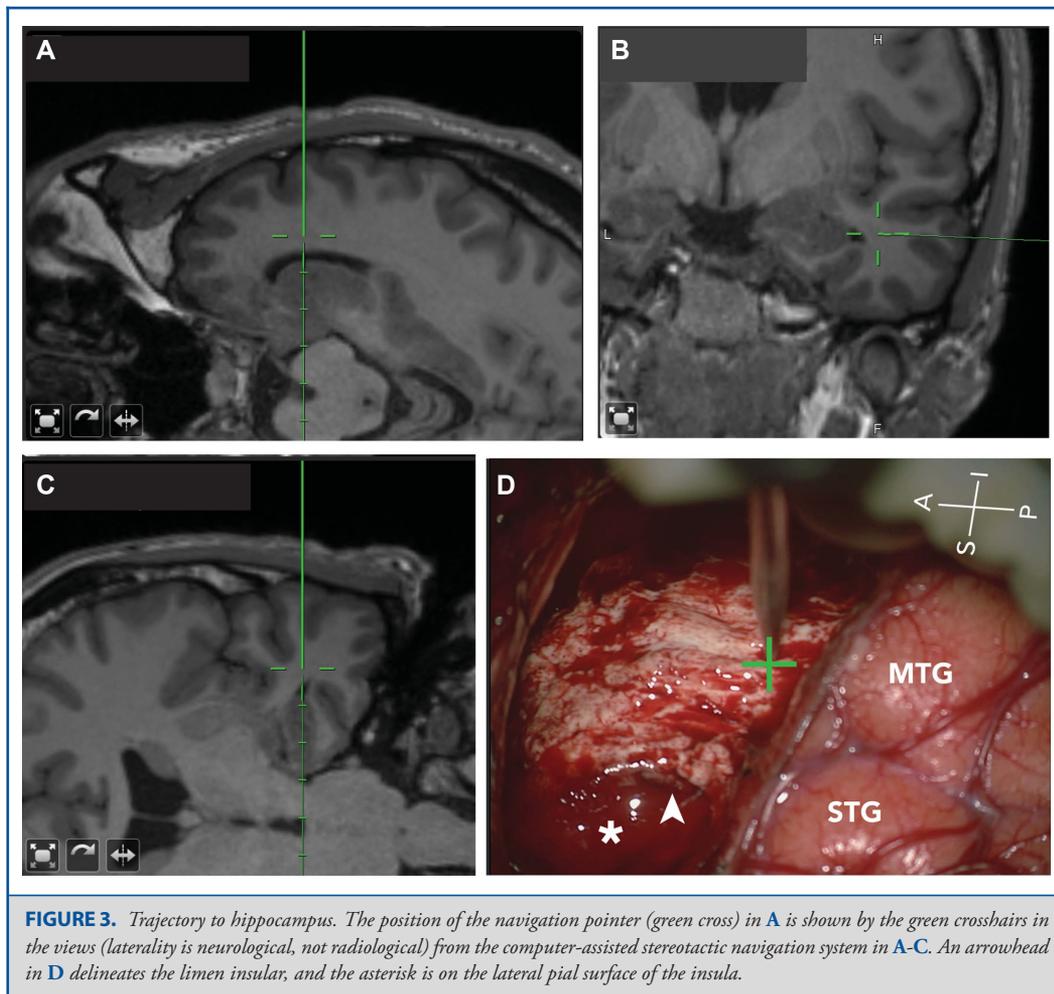


FIGURE 2. Insular landmarks. The green crosshairs in the views from the computer-assisted stereotactic navigation system in **A** and **B** indicate the position of navigation pointer (green cross) in **C**, which is positioned at the junction of the insula and limen insula. Arrowheads in **C** delineate the limen insula. The crosshairs in the views (laterality is neurological, not radiological) from the computer-assisted stereotactic navigation system in **D**, **E**, and **F** indicate the position of the pointer (green cross) in **G**. The blue asterisk in **C** and **G** marks the lateral pia of the insula, and the white asterisks mark the anterior pia of the insula.

Cortical tissue is left adherent to the sylvian fissure arachnoid at this stage.

The second anatomic compartment removed is the extrainsular compartment, comprised of all remaining temporal lobe tissue anterior and lateral to the surface of the insula. Subpial removal of the superior temporal cortex begins at the level of the posterior boundary for superior temporal gyrus (STG) resection and continues anteriorly along the sylvian fissure arachnoid and mesially to the junction of the sylvian fissure arachnoid and the pia of the insular cortex. Once the pia of the insula is discovered, gentle suction is used to expose the entire surface of the insula

to the level of the limen insula inferiorly. The limen insula is identified as the point in which the STG grey matter overlying the insula transitions to white matter going under the insula; it is the point where the surgeon can no longer peel the temporal cortex off the insular pia (Figure 2). Inferior to the limen insula, the remaining lateral temporal cortex is resected in a plane extended across the insular cortex as the mesial boundary of the resection at this stage because deeper tissue removal through the limen insula will damage Meyer’s loop. Exposure of the insula is continued from its lateral to anterior surface until the pia of the sylvian fissure is encountered along the sphenoid ridge. Full



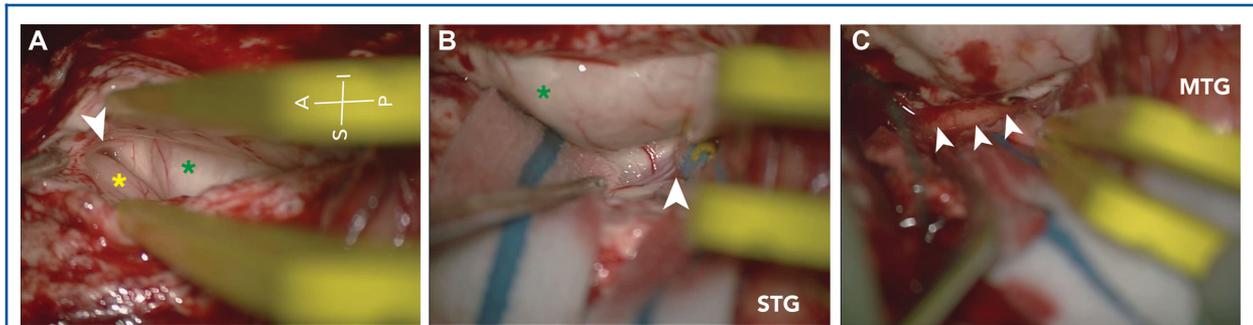


FIGURE 4. Separation of amygdala from hippocampus. The junction of the amygdala (yellow asterisk) and hippocampus (green asterisk) is indicated by the arrowhead in **A**. The inferior choroidal point (arrowhead) is visible in **B**. Linear disconnection (arrowheads) of the amygdala and hippocampus through the uncus to the pia of the crural cistern is shown in **C**.

exposure of the pia of the insula provides landmarks for subsequent stages (Figure 2). The remaining cortical tissue of the temporal pole is removed to the level of the dural incisura.

The third anatomic compartment removed is the amygdala. The white matter of the middle temporal gyrus is identified (Figure 3), through which a slit is made and extended mesially until the ventricle is encountered. Care should be taken not to undercut the temporal stem toward the insula, which will damage Meyer's loop. The junction of the amygdala and hippocampus is identified (Figure 4). Bipolar cautery and suction are used to disconnect the fused amygdala and hippocampus, creating a transection line down into the uncus until the pia of the crural cistern is encountered. The pia is exposed along this line from the dural incisura anteriorly to the inferior choroidal point posteriorly. For these and subsequent steps, the use of fixed retractors is not necessary, as adequate visualization can be obtained through a combination of bed adjustments and the use of a mouth-switch to control the operating microscope.

The landmark for the superior extent of the resection of the amygdala is often described as an imaginary line from the inferior choroidal point to either the internal cerebral artery terminus¹⁴ or the middle cerebral artery bifurcation.^{18,19} Full exposure of the insular pia, however, allows one to use the junction of the anterior pia of the insula and the limen insula as this boundary (Figure 5). After identifying the inferior choroidal point, this line can be demarcated on the surface of the amygdala and incised to open the ependyma overlying the amygdala, followed by deepening this incision linearly with suction, until the pia of the crural cistern is encountered, including the pia previously exposed during separation of the amygdala from the hippocampus. The mesial portion of the amygdala is freed by peeling it anteriorly off the pia.

The fourth anatomic compartment removed is the remaining fusiform and parahippocampal gyri to the level of the incisura. The lateral border of the hippocampus in the inferior horn of the ventricle is identified and tissue is resected in the inferior direction until the incisura is encountered. Removal of this compartment isolates the hippocampus and parahippocampal gyrus as the

only remaining structures in the planned resection, facilitating extrapial removal.

The fifth anatomic compartment, comprised of the head and most of the body of the hippocampus, is removed in extrapial fashion (Figure 6). A straight vertical shelf should extend from the intact lateral cortex to the ventricle in order to maximize exposure of the hippocampus. Next, the posterior boundary of the en bloc hippocampal resection is demarcated, and the hippocampus and parahippocampal gyrus are transected using bipolar cautery and suction until the pia of the ambient cistern is encountered and connected inferiorly to the pia overlying the dural incisura. The fusiform/parahippocampal pia is inspected to ensure that no arteries traveling to the posterior temporal lobe are at risk and then is cauterized and cut open over the middle fossa floor, stopping at the incisura. The fimbria is disconnected along the choroidal fissure, from the cut boundary of the posterior hippocampal body anteriorly, until the posterior choroidal artery and oculomotor nerve are visible through the pia. The pia along the anterior middle fossa floor, just anterior to the anterior-most portion of the parahippocampal gyrus, is cut to the level of the dural incisura.

The mesial pia is opened into the ambient cistern and the arachnoid attaching the hippocampus superiorly along the choroidal fissure is cut (Figure 7). Next, in extrapial fashion, the hippocampus is dissected free of attachments to the hippocampal fissure, posterior cerebral artery (PCA), anterior choroidal artery, and hippocampal branches of the basal vein of Rosenthal. Operating directly over the crus cerebri during this stage, no surgical instruments should come into contact with the cerebral peduncle. Inadvertent venous bleeding should be treated with irrigation and gentle pressure, rather than cautery. Final extrapial detachment requires rotating the hippocampus medially, by grasping the pial flap created in the previous steps, to expose the arachnoid of the ambient cistern along the length of the dural incisura. Opening this arachnoid allows good visualization of the P2 segment of the PCA running underneath the hippocampus, the separation of which from the hippocampus requires cauterizing and cutting feeding branches, after visual verification that

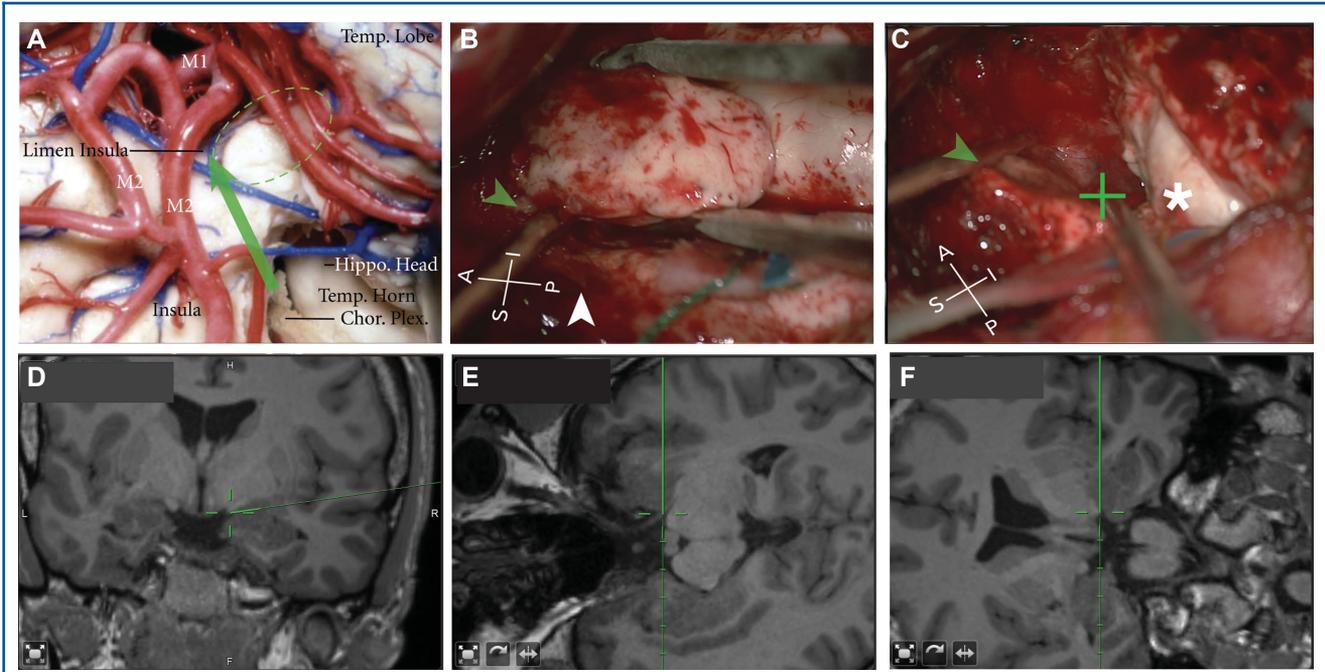


FIGURE 5. Removal of amygdala. The limen insula is identified by the dashed green circle in **A** (image in **A** adapted from Kucukyuruk et al,¹⁹ 2012 [<https://www.hindawi.com/journals/ert/2012/769825/#copyright>] under CC BY 3.0 license [<https://creativecommons.org/licenses/by/3.0/>]), in which the green line indicates a line connecting the inferior choroidal point to the junction of the anterior pia of the insula and the limen insula. This point is depicted by the green arrowheads in **A-C**. A corresponding line can be demarcated on the surface of the amygdala and followed in the mesial direction until the pia of the crural cistern is encountered, and after the mesial portion of the amygdala is freed by peeling it anteriorly off the pia, it can be removed en bloc **B**. After removal of the amygdala **C**, the position of pointer on the pia lateral to the crural cistern (green cross) is indicated by the green crosshairs in the views (laterality is neurological, not radiological) from the computer-assisted stereotactic navigation system in **D-F**.



FIGURE 6. Isolation of hippocampus. The isolated hippocampus (white asterisk) is shown in **A**. The pia over the middle fossa floor (blue asterisk) is cut posteriorly **B** and anteriorly **C** to the level of the incisura.

these branches supply only the hippocampus. Thalamoperforator arterial branches looping toward the hippocampus from both the anterior choroidal and P2 arteries must not be injured. This potential complication is avoided by dividing an artery only after visual inspection reveals perforation of the hippocampal tissue, in addition to scrupulous microsurgical technique. The trochlear nerve, which runs under the dural incisura, must not be inadvertently stretched by over-manipulating arachnoid attachments during the extrapial dissection. Once the hippocampal head and

body are completely free of all attachments, the specimen can be lifted out en bloc (Figure 7E and 7F).

The last anatomic compartment removed is the tail of the hippocampus. The bed is rotated to allow visualization of the hippocampal tail to the point where it meets the calcar avis, the inferior prominence on the medial wall of the atrium of the lateral ventricle¹⁴ (Figure 8). Maximum rotation results in adequate visualization of the posterior-most extent of the mesial resection without having to transect and retract the occipi-

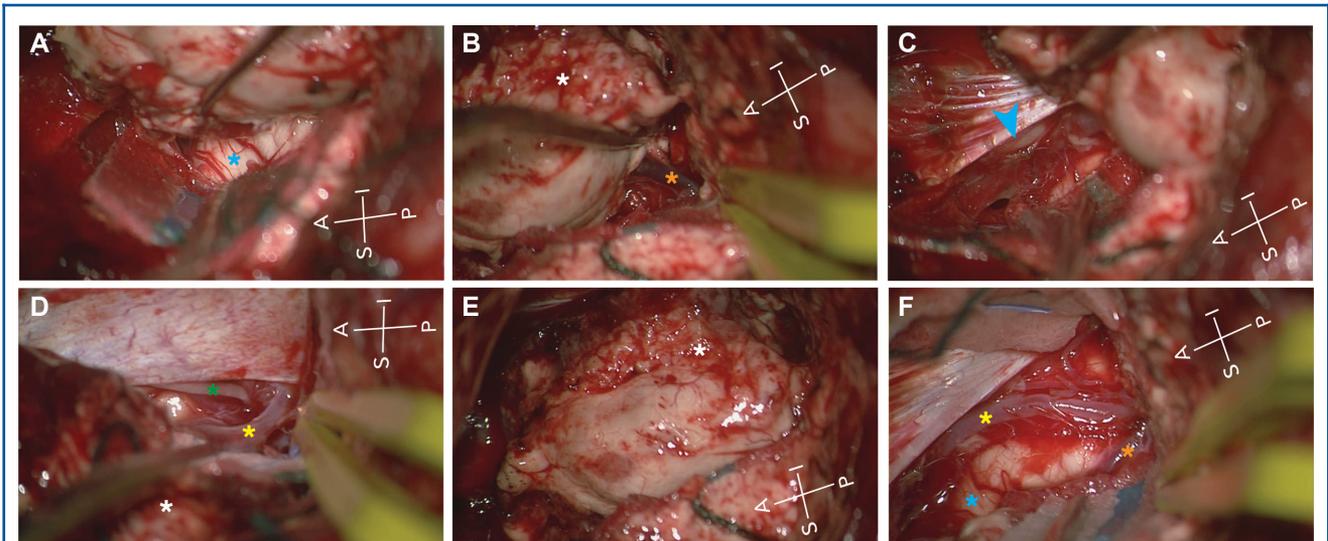


FIGURE 7. Extrapial resection of hippocampus. Opening the pia below the fimbria reveals the cerebral peduncle (blue asterisk **A**). Posterior disconnection will reveal the basal vein (orange asterisk in **B**, white asterisk indicates parahippocampal gyrus). Anteriorly, the third nerve is visualized (blue arrowhead **C**), whereas posteriorly the fourth nerve may have been seen coursing under the incisura (green asterisk **D**). The hippocampus is disconnected from branches of the PCA (yellow asterisk) from the ambient cistern **D**. After complete disconnection of the vascular supply and pial attachments of the hippocampus **E**, it can be removed en bloc, allowing complete visualization of the ambient cistern **F**.

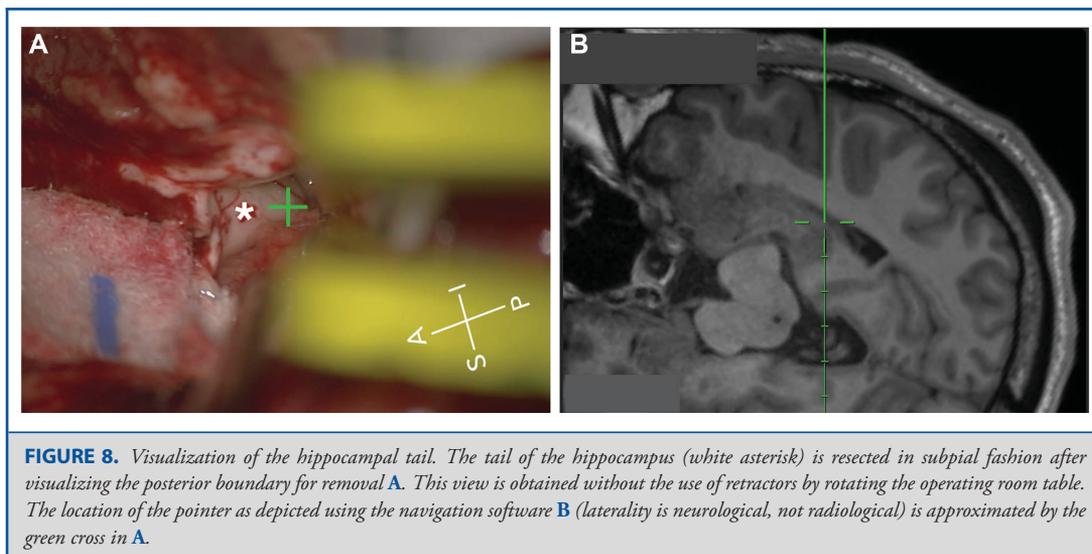
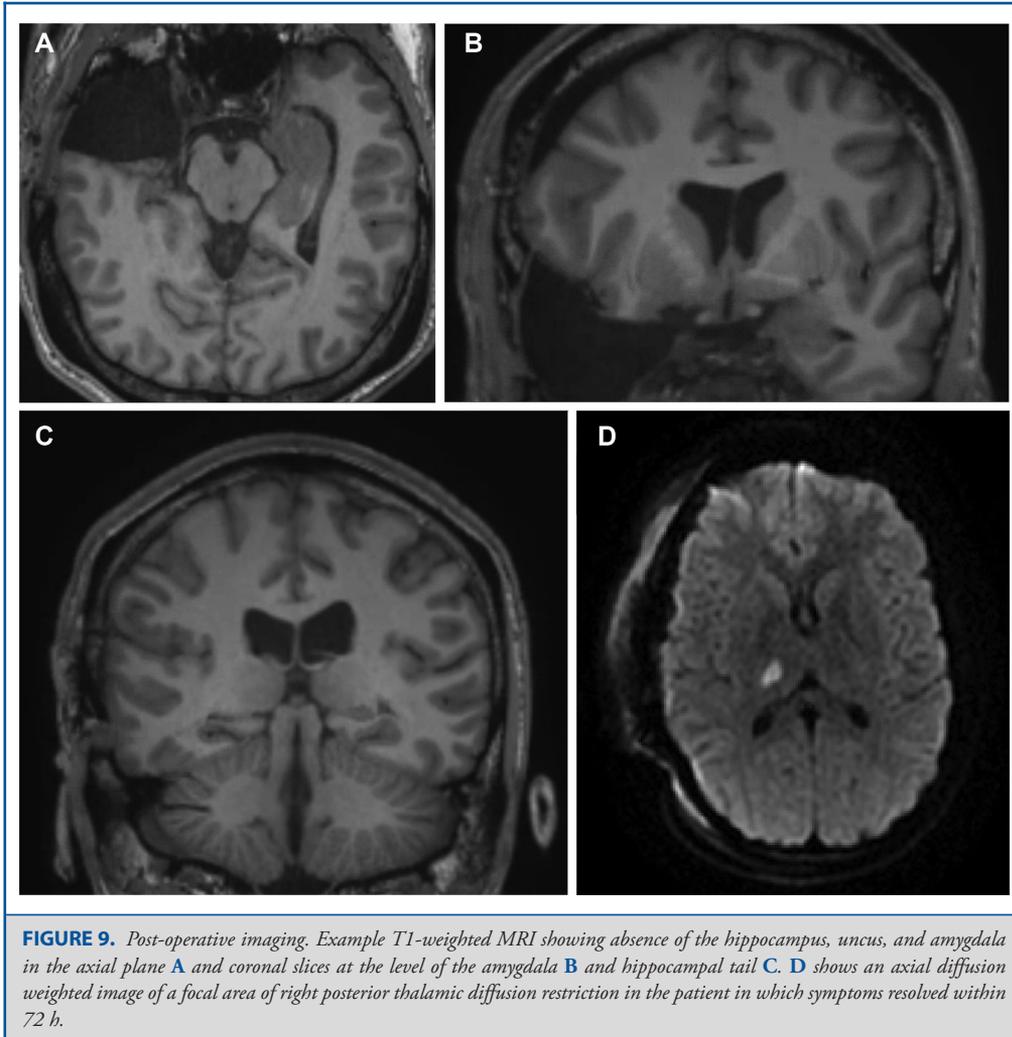


FIGURE 8. Visualization of the hippocampal tail. The tail of the hippocampus (white asterisk) is resected in subpial fashion after visualizing the posterior boundary for removal **A**. This view is obtained without the use of retractors by rotating the operating room table. The location of the pointer as depicted using the navigation software **B** (laterality is neurological, not radiological) is approximated by the green cross in **A**.

totemporal fasciculus as described by Spencer et al.¹² After identifying the cut edge of the hippocampus and assuring that the pulvinar is protected with a cottonoid over the choroid plexus, the tail of the hippocampus is resected in subpial fashion to the level of the quadrigeminal plate, leaving the arachnoid of the ambient and quadrigeminal cisterns intact. Figure 9A shows the postoperative MRI appearance of the resection.

Clinical Outcomes

A total of 62 patients (31 females) met inclusion criteria. Table 1 shows patient characteristics, none of which were statistically correlated to seizure outcome or postoperative complications. Four patients developed an unexpected postoperative complication, and there were no deaths. One patient developed an infection requiring reoperation (1.62%; 1/62). Two patients had temporary contralateral upper extremity motor weakness,



one resolving within 72 h and the other resolving within 1 mo. For these 2 subjects, plus an additional subject without symptoms, postoperative MRI demonstrated posterior thalamic infarcts (3/62, 4.8%; example in Figure 9B-9D). Eleven subjects (17.7%) reported a postoperative quadrantanopia. Despite our standard practice of obtaining preoperative visual field testing in all temporal lobe surgery patients, few patients underwent the recommended postoperative evaluation.

The mean interval between ATL and the last follow-up visit was 24.6 mo (median = 30, interquartile range = 12.3-35.8). Kaplan-Meier analysis (Figure 10) demonstrated that 93.5% of patients achieved seizure freedom (Engel class I) in 12 mo, and 62.9% remained seizure free at longest follow-up (40 mo, see Table 2). The percentage of patients with favorable outcome (Engel class I/II) was 95.2% (CI = 85.7-98.4%) at 1 yr and 85.5% (CI = 75.0-92.2) at 40 mo.

Operative times were not collected in the surgical database from which this study was derived, but our impression is that

a reasonable trade-off exists between extra time required for the extrapial portion of the resection and time saved by efficient completion of the prior steps using the compartmentalization approach. Of interest, in 1 patient who had undergone laser interstitial thermal therapy (excluded from analysis because of prior surgery), the extrapial approach was found to be facilitated by postablation vascular diminution.

Research Outcomes

En bloc specimens were obtained in each case (see example in Figure 11), with a portion sent for clinical neuropathology evaluation and a portion banked for further neuroscientific analysis. Extrapial dissection of the hippocampus by avoiding undue damage to the hippocampal sulcus facilitated preservation of the subiculum and tri-synaptic hippocampal pathway for further analyses. This technique enabled development of an innovative confocal microscopy technique to quantify protein changes at the level of individual boutons on the soma of dentate granule

TABLE 1. Patient Characteristics

| | |
|--|------------------|
| Mean age (years) | 22.6 (13.5-32.5) |
| Mean duration of epilepsy (years) | 21.5 (8.6-30.6) |
| Mean age at the time of surgery (years) | 44.4 (34.3-53.6) |
| Risk factors (# subjects) | |
| Congenital/perinatal | 18 (29%) |
| Acquired | 24 (39%) |
| Congenital and acquired | 10 (16%) |
| None | 10 (16%) |
| MRI characteristics (# subjects) | |
| Nonlesional | 29 (46.8%) |
| Hippocampal sclerosis | 25 (40.3%) |
| Focal cortical dysplasia | 3 (4.9%) |
| Hippocampal sclerosis and focal cortical dysplasia | 2 (3.2%) |
| Heterotopia | 1 (1.6%) |
| Post-traumatic gliosis | 1 (1.6%) |
| Prior intracranial monitoring (# subjects) | |
| None | 37 (59.7%) |
| Stereo-electroencephalography | 14 (22.6%) |
| Subdural electrodes | 11 (17.7%) |
| Histopathological findings | |
| Hippocampal sclerosis | 32 (51.6%) |
| Focal cortical dysplasia | 6 (9.7%) |
| Heterotopia | 3 (4.9%) |
| Nonspecific | 21 (33.9%) |

neurons^{20,21} and an ex vivo 11.7T MRI technique to achieve mesoscale resolution of fiber tracts connecting different layers of the hippocampus (Figure 12)²² and demonstration of aberrant connectivity between the granule cell layer and stratum moleculare.^{23,24}

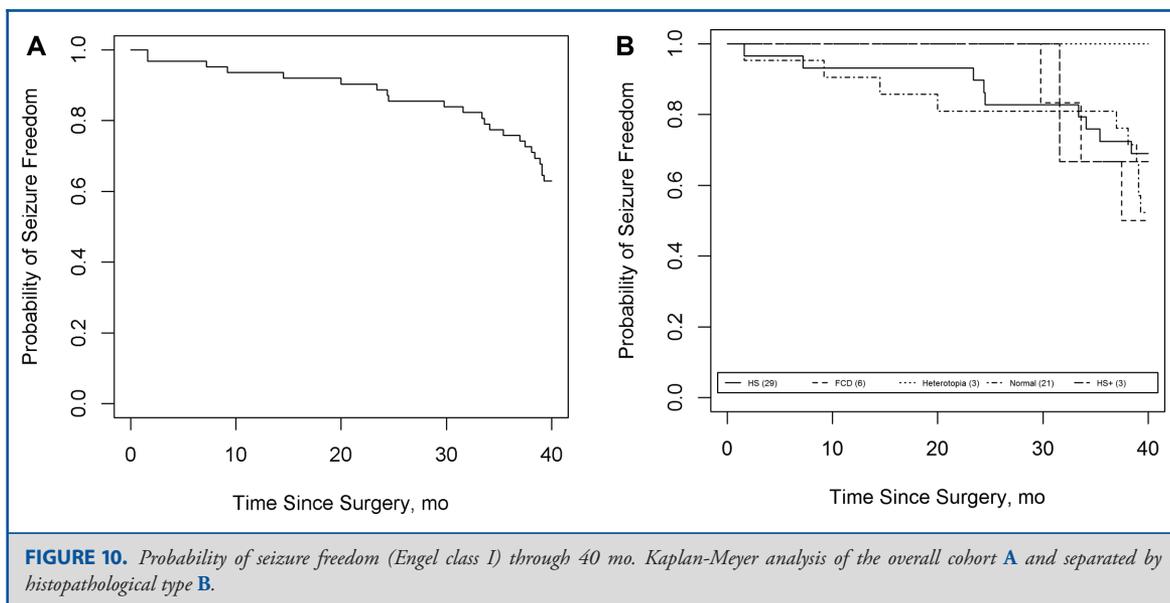
TABLE 2. Seizure Outcomes

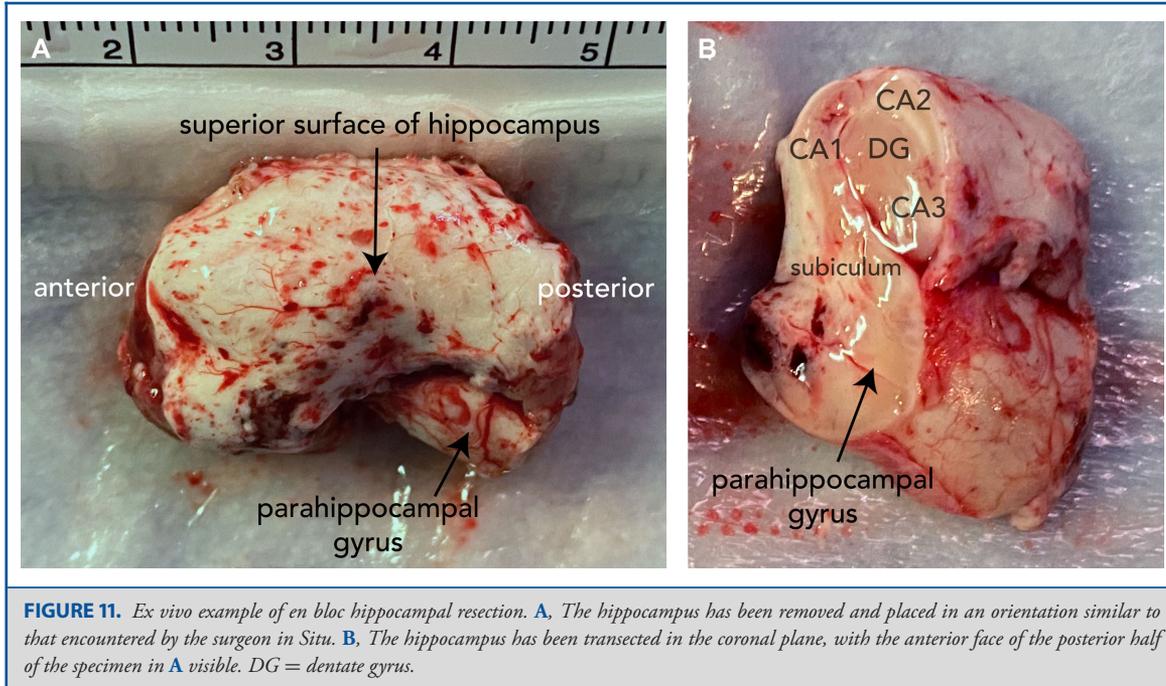
| Month | No. with follow-up | Engel I % (CI) | Engel I + II % (CI) |
|-------|--------------------|------------------|---------------------|
| 6 | 53 | 96.8 (87.7-99.2) | 96.8 (87.7-99.2) |
| 12 | 48 | 93.5 (83.7-97.5) | 95.2 (85.7-98.4) |
| 18 | 46 | 91.9 (81.7-96.6) | 93.5 (83.7-97.5) |
| 24 | 41 | 88.7 (77.8-94.5) | 93.5 (83.7-97.5) |
| 30 | 36 | 83.9 (72.1-91.0) | 90.3 (79.7-95.5) |
| 36 | 30 | 75.8 (63.1-84.6) | 88.7 (77.8-94.5) |
| 40 | 30 | 62.9 (49.7-73.6) | 85.5% (75.0-92.2) |

Probability of Engel class at multiple postoperative durations, with 95% CI. Number with follow-up denotes patients with known Engel class at the given postoperative months. Last observation carried forward was used for patients without sufficiently long follow-up durations.

DISCUSSION

We demonstrated that an extrapial approach to hippocampectomy can be performed safely. The primary risk involved is that of vascular injury when performing microvascular detachment of the hippocampal arterial supply from the cisternal space. Of the patients, 4.8% exhibited MRI evidence of interruption of minor vascular supply to the thalamus, likely from injury to a perforating artery from the PCA; 2 experienced temporary weakness and 1 was asymptomatic. These results compare favorably to the rates of infarct reported in other studies of temporal lobectomy. Engel et al³ reported findings on postoperative MRI suggestive of ischemic changes in 3/15 patients (20%), with 1/5 (6.7%) experiencing a temporary clinical manifestation and no permanent morbidity. Wiebe et al⁴ reported a symptomatic thalamic infarct in 1/40 patients (2.5%), Sindou et al²⁵ reported anterior choroidal artery territory ischemia





associated with mild permanent hemiparesis in 2/100 patients (2%), and Heller et al²⁶ reported a stroke in 5/55 temporal lobectomy patients (9.1%), 3 of whom (5.5%) had permanent deficit.

Nearly 94% of patients in our cohort were seizure free (Engel class I) 12 mo following surgery, with 89% and 63% remaining seizure free at 24 mo and 40 mo, respectively. These outcomes compare favorably with those from randomized-controlled trials for temporal lobectomy: Wiebe et al⁴ reported 58% of patients achieving Engel class 1 at 1 yr, Schramm et al²⁷ reported 74% at 1 yr, and Engel et al³ reported 73% of patients achieving Engel class 1 at 2 yr. Our outcomes also compared favorably to those from a recently reported large case series of selective amygdalohippocampectomy in which 58% of patients achieved Engel class 1 at 1 yr,²⁸ a prospective long-term outcome study in which 63% of patients achieved Engel class 1 at 2 yr,²⁹ and 2 large retrospective cohort studies in which 55%³⁰ and 72%³¹ of patients achieved Engel class 1 at 2 yr.

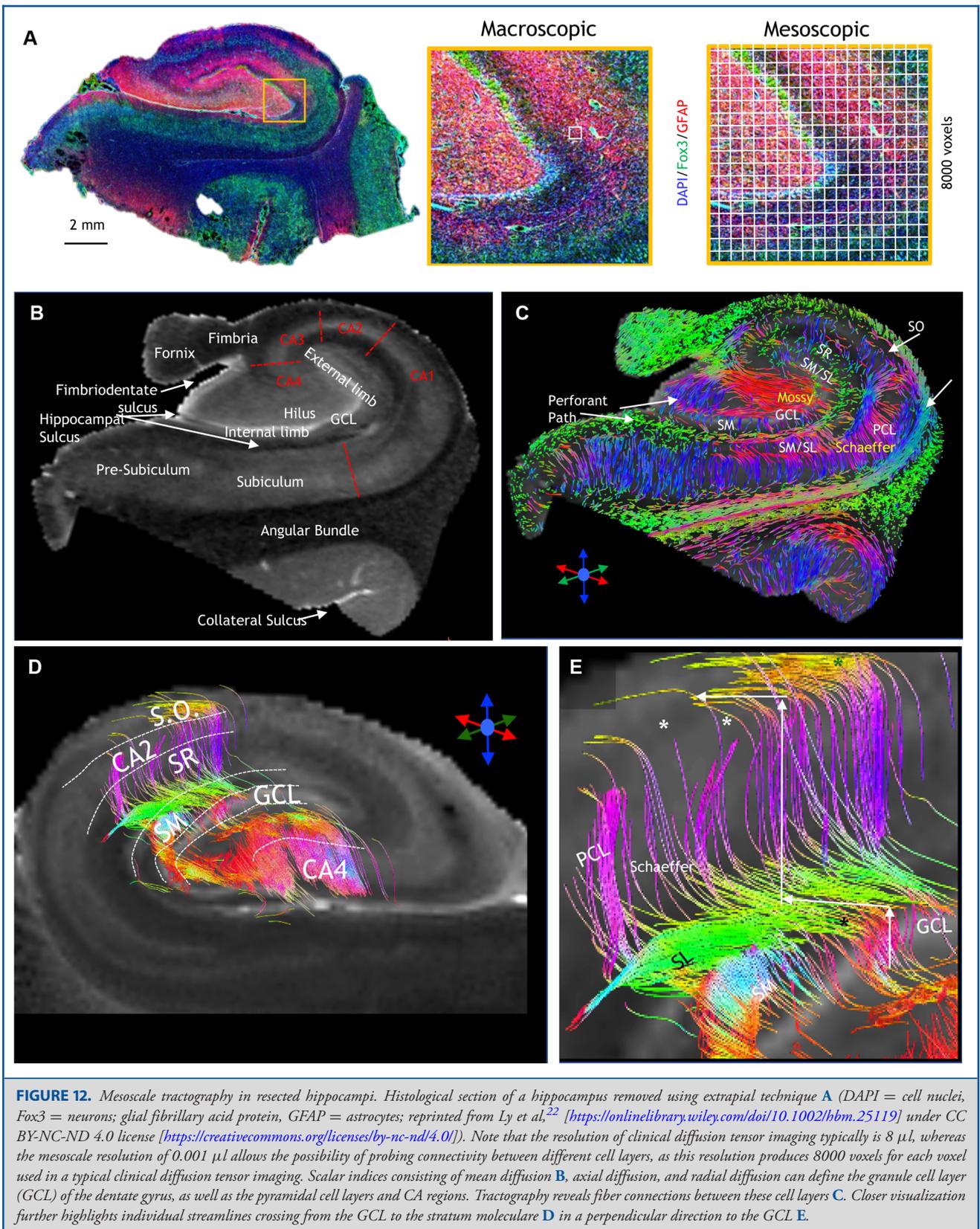
Complete resection of the hippocampus enabled by the extrapial technique may have facilitated these favorable seizure outcomes. Classic descriptions of hippocampal removal involve a subpial approach, using ultrasonic aspiration to disconnect the fimbria and aspirate the subiculum, then lifting the hippocampus to reveal attachments to the hippocampal sulcus, which are then divided.³²⁻³⁴ The hippocampal sulcus is capped by the cornu Ammonis (CA) regions and divides these from the dentate gyrus on its superomesial surface. Thus, the subpial approach usually

results in leaving residual hippocampal tissue that is then aspirated from the sulcus. In the extrapial approach, there is no risk of inadvertently leaving behind portions of the hippocampal body.

Preservation of the dentate gyrus and hippocampal subfields in specimens resected using this technique also highlight the fact that there is much unexplored territory in the application of modern imaging techniques to anatomical specimens, at both the micro- and meso-scales. Anatomic specimens from patients remain the only way to link noninvasive imaging to ground truth regarding the cellular substrate of the imaging signal of interest. Preservation of the hippocampus using an extrapial resection approach facilitated the development of ex vivo mesoscopic diffusion MRI to study the epileptic human hippocampus,²²⁻²⁴ a technique with potential to help bridge the gap between histopathological analyses and diagnostic radiology and provide unique insights into epilepsy pathophysiology.

CONCLUSION

Extrapial en bloc hippocampal resection is safe, results in seizure freedom rates at the high end of the range reported previously from descriptions of previous techniques for ATL, and may facilitate optimal preservation of the specimen for subsequent study, an important consideration in an era of increasing use of minimally invasive approaches.



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