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Original Article

Ultrasound-Navigated Multiple Hippocampal Transections: An Anatomical Study

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Abstract

Background Multiple hippocampal transection (MHT) is a surgical technique used for the treatment of drug-resistant mesial temporal lobe epilepsy in situations where standard procedures would pose a high risk for memory deterioration. During MHT, the longitudinal fibers of the hippocampus, implicated in epilepsy spreading, are interrupted, while the transverse memory circuits are spared. The extent of MHT is governed by intraoperative electrocorticography; abolition of epileptic discharges serves as an end point to terminate the transection. In other words, the aim of MHT is not the anatomical completeness of hippocampal transection. In contrast, we hypothesize that only the complete transection of hippocampal cross-section is needed to durably terminate epilepsy, avoiding possible postoperative reorganization of longitudinal pathways. Here, we report an anatomical study designed to evaluate the feasibility of complete transection of hippocampus with the aid of ultrasound neuronavigation and we propose new instruments to reach this goal.

Methods Five cadaveric brains were analyzed in this study. MHT was performed on both sides of each brain either with or without ultrasound neuronavigation. The percentage of transected cross-section of the hippocampus was measured using magnetic resonance imaging (MRI) and both sides were compared.

Results The ultrasound-guided MHTs were more likely to achieve complete hippocampal transection compared with the nonnavigated MHT transection (73 vs 58%; $p < 0.01$). Our study also allowed us to propose specialized transectors to minimize invasivity of this procedure.

Conclusion Completeness of MHT can be better reached with the aid of an ultrasound neuronavigation system; modified instruments for this procedure were also designed.

Keywords
- temporal lobe
- epilepsy
- multiple hippocampal transection
- memory
- ultrasound guidance

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Introduction

Temporal lobe resections are the most widely performed epilepsy surgeries in adults. These procedures include standard anteromesial temporal lobe resection[1] and several modifications of amygdalohippocampectomy.[2] Both good postoperative seizure outcomes and low risk of surgical complications have been reported.[3] Nevertheless, the temporal lobe epilepsy surgery is underutilized worldwide.[4] One of the reasons for this fact are attending physicians' or patients' concerns about postoperative cognitive function decline, especially after operations on language-dominant side in patients with morphogically normal hippocampus and intact memory. Thus, there is a strong mandate for an ongoing search for minimally invasive nondestructive procedures. Hypothetically, there are two ways to improve functional outcomes after temporal lobe epilepsy surgery: (1) minimize collateral damage in the access route (e.g., laser thermal ablation)[5] and (2) minimize destruction to the target and restrict the intervention only to structures important for seizure generation, early propagation, and synchronization.[6]

One possible way to combine both the points is to utilize multiple hippocampal transection (MHT). The principle of this operation is based on observations that both interictal and ictal epileptic discharges in hippocampus spread and synchronize by means of anterior-to-posterior propagation via the longitudinal hippocampal fibers.[7] Thus, transection of these fibers, if performed perpendicularly to the long axis of hippocampus, has the potential to stop seizures while keeping intact the transverse circuits. MHTs have been performed in small groups of nonlesional temporal lobe epilepsy patients[8] and patients with amygdala enlargement[9] with encouraging results.

In all of the published series, the main acute procedural end point was the abolition of spikes on perioperative intracranial electocorticography (iECoG). Once these changes were observed, the surgery was terminated; hence, the real extent of the transections was not studied in detail.[10] Whether abolition of iECoG epileptic discharges is a valid procedural end point (especially since these iECoG changes may only be transitory) is debatable.[11–13]

In contrast, we hypothesize that the completeness of intrahippocampal longitudinal fiber transection is the crucial factor for seizure control in mesial temporal lobe epilepsy treated with MHT. With this premise in mind, we conducted an anatomic study of a cadaveric brains, in which we aimed to achieve complete transections of the hippocampal body perpendicular to the long axis except fimbria. On one side, we performed hippocampal transection based solely on anatomical landmarks, while on the contralateral side we employed a perioperative ultrasound examination of a navigational adjunct. The basic null hypothesis was that there was no difference in the extent of transection on both sides.

In addition, we used this anatomical study to design and develop specific shapes and sizes of several transectors to facilitate precise and minimally invasive hippocampal transections.

Material and Methods

In this anatomical comparative study, we have performed MHT in five formalin-fixed human cadaveric brains supplied by our institute's pathology department. The study took place at a tertiary referral hospital with an epilepsy surgery program during a 2-year period (2020–2021).

During the cadaveric surgery, the middle temporal gyrus was resected, and via a large corridor through white matter on the bottom of the gyrus, the temporal horn of the lateral ventricle was approached on both sides of the brain. The head and body of the hippocampus were well exposed (►**Fig. 1**).

After this step, the parameters of the hippocampus were measured and registered by ultrasound examination (Craniotomy probe 8862, 4–10MHz, Ultrasound BK Medical Flex Focus 800, BK Medical A/S, Herlev, Denmark) (►**Fig. 2**). The transection procedure followed. The first two transections of

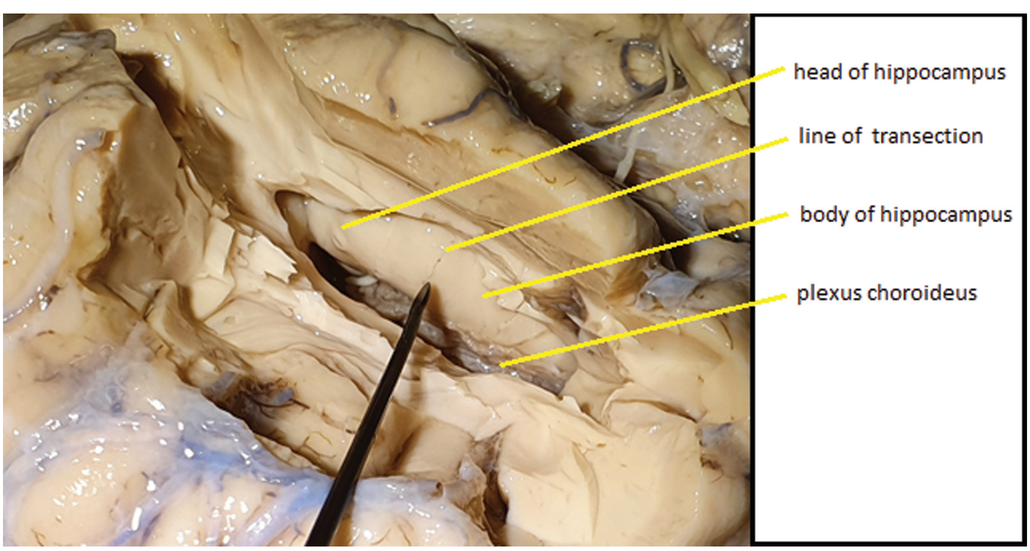

Fig. 1 Exposure of the head and body of the hippocampus via the middle temporal gyrus.

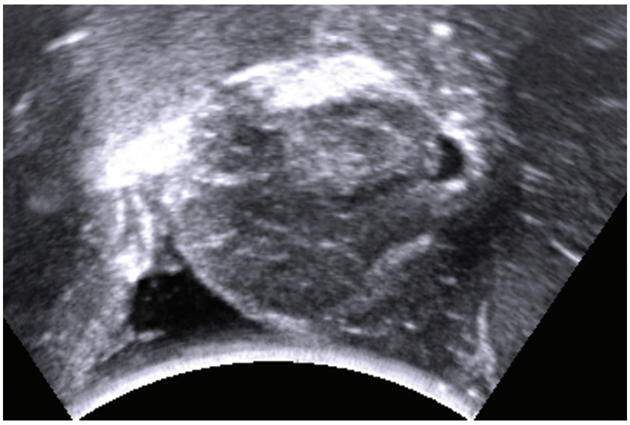

Fig. 2 Ultrasound examination of the hippocampus (images oriented similarly to coronal magnetic resonance imaging scans).

the hippocampus were executed at the level of the hippocampus head followed by three or four transections of the hippocampus body. The spacing between each transection was 5 mm. The aim of each transection was to completely transect the hippocampus perpendicularly to its long axis, hence interrupting all of the longitudinal hippocampal connections except fimbria that could be easily visualized during the surgery and injury of it could be avoided. On one side of the brain, the transections were performed based on visible anatomical landmarks and according to the pretransection ultrasound examination (control group). On the other side of the same specimen, the transections were governed by ultrasound guidance during each transection so the transector could be visualized while inserted in the hippocampus (study group) (►**Fig. 3**). The side that was transected under ultrasound supervision was assigned randomly for each cadaver to enable blinded reading by radiologist.

The transectors that were designed by the first author (J. S.) include bayonet loop curettes (►**Fig. 4a**). The loop has different diameter and can be chosen according to the size of hippocampus cross-section (►**Fig. 4b**). A 6-mm-diameter loop is used for the head and proximal part of hippocampus, and a 4-mm loop for the subiculum. The dorsal part and tail of the hippocampus is transected by 4-mm transectors that have

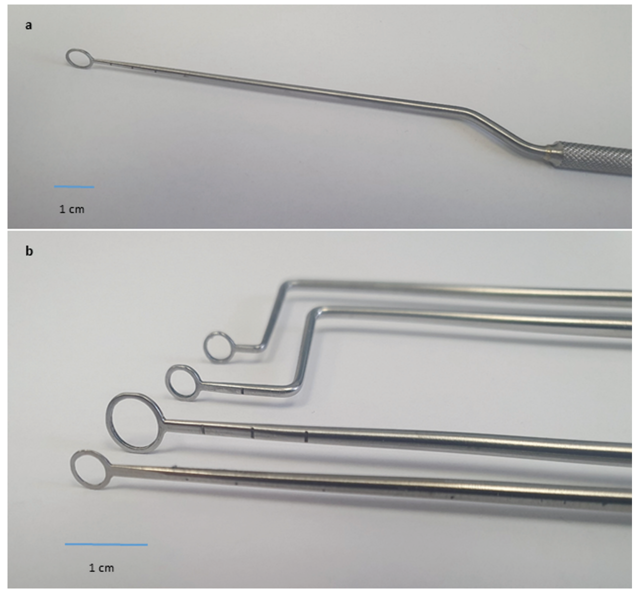

Fig. 4 Transectors. (**a**) Straight transector overview. (**b**) Different types of transectors' tips in detail: 4-mm straight loop for subiculum transection, 6-mm straight loop for transection of the head and proximal body of hippocampus, and 4-mm bended loop for transection of the distal hippocampal body and tail.

extra bend designed to facilitate access. The edge of the loop is slightly blunted to enable the surgeon to feel the resistance of the pia mater and the arachnoid layer, thus avoiding injury to deeply located ambient cistern structures. The cadaveric surgery was performed solely by the first author (J. S.).

Postoperative MRI Scans

After surgery, we scanned the cadaveric brain with magnetic resonance imaging (MRI) and measured and calculated the percent transected cross-sectional area of each transection. MRI was performed using a 3T Siemens Skyra (software VE11C, Siemens, Erlangen, Germany) scanner equipped with 20-channel head and neck coil (to accommodate the plastic container with the cadaver) using 3D magnetization-prepared rapid gradient echo T1-weighted sequence (slice thickness:

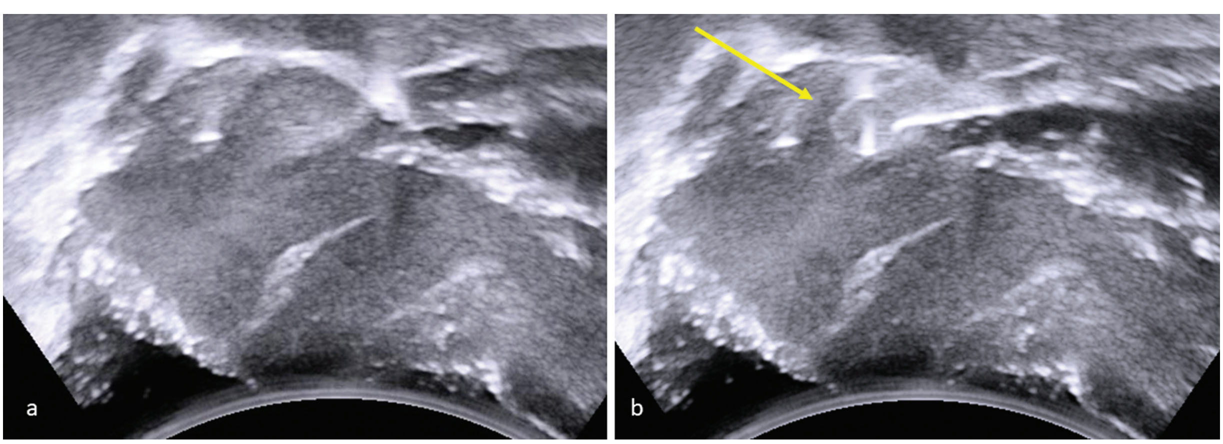

Fig. 3 Ultrasound examination of hippocampus without (**a**) and with (**b**) transector (*arrow*) placed in the hippocampus.

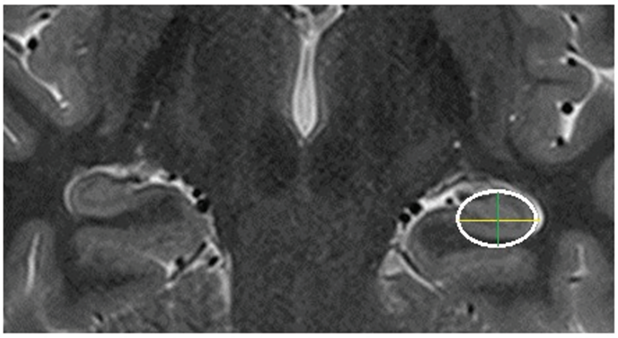

Fig. 5 The surface of the planned and realized transections can be estimated and calculated by approximating this region to an ellipse (*white ellipse*: cross-section of hippocampus, *yellow line*: diameter *a*; *green line*: diameter *b*).

1.1 mm; inplane resolution: 0.9 × 0.9 mm; TR: 1,540 ms; TE: 2.48 ms; TI: 900 ms; FA, 8 degrees) and T2-weighed sequences in the sagittal plane, oblique transverse plane aligned with the long axes of both hippocampi, and oblique coronal plane perpendicular to this plane. All three T2-weighted sequences shared common parameters—slice thickness: 2 mm; TE: 82 ms; TI: 5,160 ms; NEX 2: 2 concatenations with zero interslice gap; 871 phase-encoding steps; ETL: 15; inplane resolution 361 × 361 µm interpolated to 181 × 181 µm (matrix 1,024 × 1,024 pixels).

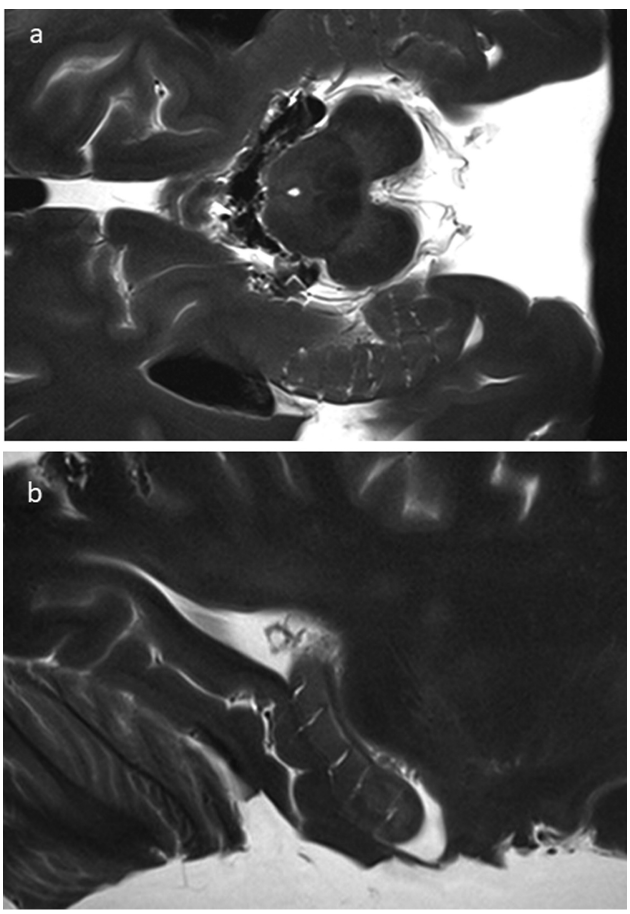

Fig. 6 Transection visible on the cadaveric brain magnetic resonance imaging in the (**a**) axial plane and (**b**) sagital plane.

When imaged in the coronal plane, the shape of the cross-section of the body of the hippocampus (perpendicular to the long axis of the hippocampus) can be approximated as an ellipse (►**Fig. 5**).

Therefore, the surface of this cross-section can be calculated using two diameters directly measured on the MRI, using the following expression: $S = a/2 \times b/2 \times \pi$. Here, a is the diameter of the hippocampus body in axial plane, while b is its diameter in sagittal plane. The diameters and the surface of the accomplished transection can be measured and calculated in a similar fashion (►**Fig. 6**); the ratio of these two surface estimates (planned and realized transection) can be expressed as percent transected area.

Statistics

Statistical analysis was performed in the SPSS statistical program from IBM, version 19. For descriptive statistics, medians and interquartile means were established. Nonparametric Mann–Whitney U test of the distribution of differences (percent of transection extent) was used for comparison of the study and control group.

Ethics

All data collection, storage, and processing were done in compliance with the Helsinki Declaration. The study was approved by the Ethical Committee of the Na Homolce Hospital. It was supported by Ministry of Health of the Czech Republic (grant MH CZ and DRO [NHH] IG 171501 and IG 193001).

Results

Each cadaver had five to six transections of the hippocampus on each side, and each transection was measured and analyzed separately. Altogether 27 transections were measured in the control group and 27 transections in the study group.

MRI measurement of transected diameters was conducted by a side-blinded radiologist (J. K.) and the comparison of the two groups was statistically evaluated.

The average cross-section of the body of the hippocampus was 53 mm^2 in the control group versus 47 mm^2 in the study group. The median percentage of transection was 58% in the control group and 73% in the study group (►**Table 1**). A Mann–Whitney test indicated statistically significant difference of distribution in favor of the study group: U ($N_{\text{control}} = 27$, $N_{\text{study}} = 27$) = 153, $Z = 3{,}641$, p (exact two-sided) = 0.0014. When evaluating each cadaver individually and comparing the control group side with the study group, we reached similar results albeit without reaching statistical significance. However, there was clear increase in the transected planes in both groups, possibly reflecting the learning curve of the surgeon. Detail results of transected ranges of the hippocampus for both groups are shown in ►**Fig. 7**.

Discussion

MHT is an epilepsy surgery performed in patients at high risk of postoperative memory decline (e.g., nonlesional mesial

Table 1 Descriptive statistics of both groups

Group	*N* (transections)	Median (percent transected area %)	Interquartile range
Control group	27	58.3	51.3–65.9
Study group: ultrasound guided	27	72.9	63.9–83.0

Note: U ($N_{control} = 27$, $N_{study} = 27$) $= 153$, $Z = 3.641$, p (exact two-sided) $= 0.0014$.

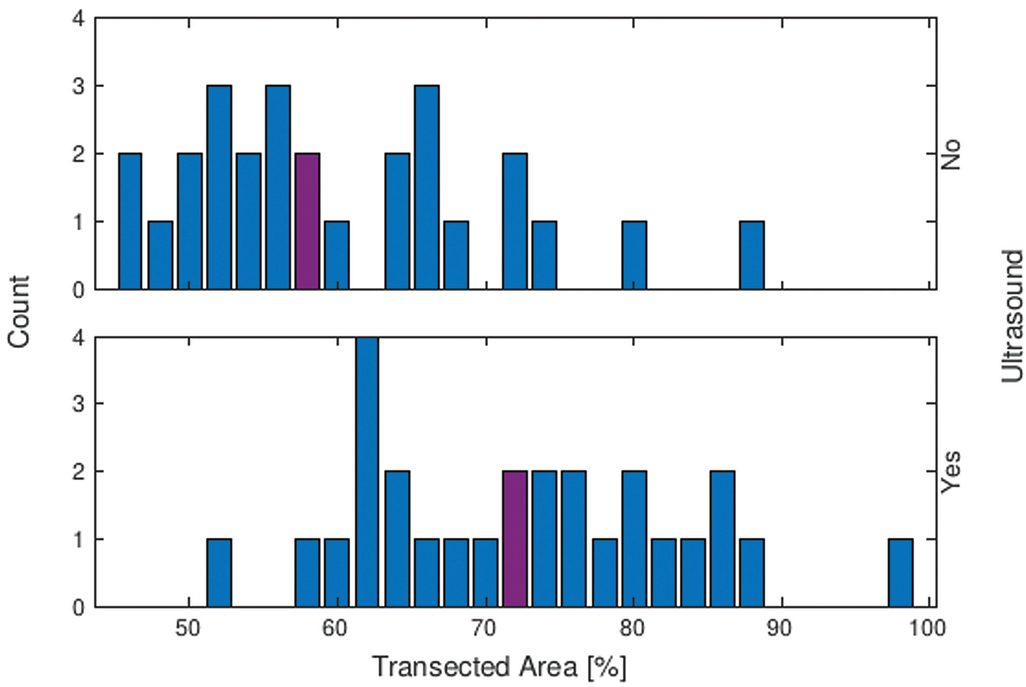

Fig. 7 The percentage of transected cross-section of the hippocampus of each transection with and without ultrasound guidance.

temporal lobe epilepsy). Some authors used MHT successfully as an adjunct to lesionectomy in patients with epilepsy due to hippocampal lesions[14] or in tandem with multiple subpial transections.[15]

The principal goal of this procedure is the disruption of the longitudinal pathway of the hippocampus, which plays a role in the synchronization and propagation of epileptic discharges, while sparing transverse lamellae, responsible for memory function.

This study was made on cadaveric brains. Its only aim is to prove that the extent of longitudinal hippocampal fibers transections is more complete when using ultrasound navigation. Thus, it has no ambition to asses how MHT will work in real surgery and if it will yield better cognitive results. Moreover, the study is based on yet unproven hypothesis that completness of longitudinal fibers transections has the potential to stop seizures while keeping intact the transverse circuits that are responsible for memory function. Furthermore, it is not clear whether this procedure lowers the risk of epileptogenic network reorganization after the operation and late seizure reccurence. To our knowledge, the extent of transections has never been studied in published clinical series.

The goal was to reach full anatomic hippocampal body transection via three or four transections, perpendicular to its long axis. We employed an ultrasound probe in the area of the body of the hippocampus and compared these navigated transections to transections based only on anatomical landmarks, i.e., without the benefit of visualizing the tip of the transector at the depth of the hippocampus. The interval spacing between each transection was kept to ~5 mm. We hypothesized that ultrasound visualization of the transector and anatomical landmarks of the hippocampus during the operation would have the potential of improving the precision of this operation. Even if executed, we did not include the transection of the head and subiculum in the analysis of our cadaver study as the surface of the these cross-sections is not possible to approximate with easy mathematical formula (as for the body of the hippocampus as ellipse); hence, the calculation would not meet adequate scientific level.

We found that ultrasound navigation led to a significantly larger extent of transections in the study group. Subjectively, the ultrasound-assisted transections in the study group allowed for much higher operator confidence than the anatomy-guided transections in the control group.

Several operative challenges had to be overcome in this study. Due to the stiffness of the formalin-fixed cadaveric tissue, our approach to the temporal horn via white matter on the bottom of superior temporal sulcus had to be wide. In a living specimen, the white matter dissection can be limited to less than 1 cm to open the temporal ventricle as needed and can be provided via well known approaches (trans-sylvian, transtemporal, transulcal). We also recognized that the white matter dissection should be limited in its dorsal extent so as to avoid damage to Meyer's loop. Furthermore, during this experiment, we encountered serious difficulties in achieving transverse transection of hippocampus in its dorsal parts (dorsal body and tail of hippocampus). Thus, we created a specifically bent transector, enabling the surgeon to reach the target in a living patient via a minimal opening in the temporal horn above the head of the hippocampus.

The most commonly used form of the MHT techniques relies on preoperative chronic intracranial video electroencephalographic monitoring to prove hippocampal seizure onset zone and intraoperative electrocorticography (iECoG) to demonstrate hippocampal spike abolition during the operation.[16]

However, it is debatable whether abolishment of ECoG spikes provides an adequate end point for these transections. Some authors considered iECoG-based guidance to be of limited value in temporal lobe epilepsy surgery.[12,13] Another group found that a high proportion (approximately one-third) of patients may not even have any spikes on their preoperative iECoG.[17]

In addition to MHT methodology, the question of the utility of adjunctive lesions also remains open. For example, some MHT case series also reported transections or resections of the parahippocampal gyrus. However, such approach remains controversial, given that the main afferent cortical connections of the polysynaptic intrahippocampal pathway project via parahippocampal gyrus and that the direct intrahippocampal pathway proceeds via the entorhinal and perirhinal cortices. In addition, the direct intrahippocampal pathway efferents communicate to the cortex via the entorhinal cortex, which can be destroyed by parahippocampal transection or resection.[18] Hence, it is our opinion that entorhinal and perirhinal cortex should be excluded from the surgery for the sake of preserving memory function.

MHT is a technique that resembles multiple subpial transections. In this technique, 62 to 71% of patients had greater than 95% seizure reduction.[19] During longer follow-up, however, only 16% were seizure-free.[20,21] The logical explantion of this fact is that the destruction of the routes of seizure propagation was incomplete and seizure recurrence is the consequence of neural network reorganization. What cannot be avoided in neocortex can be solved in hippocampus by technically feasible nearly complete transections perpendicular to the long axis of the hippocampus.

Based on the known organization of memory circuits,[18] we also hypothesized that the truly perpendicular transection to the long axis of the hippocampus is the critical condition required to avoid postoperative memory decline. However, we are aware that this model is oversimplifiyed and some memory functions are supported by connections that do not run perpendicular to long axis of the hippocampus.

That said, we recognize that some MHT authors present postoperative MRI scans in which the transection of the dorsal part and tail of the hippocampus is actually parallel to the long axis, yet the postoperative memory results are excellent.[22] Further studies are needed to reconcile these reported findings with the theory of memory circuits.

Despite several inherent limitations in our study, we think that our findings may lead to an improvement in the MHT operative technique and we plan to use it, build on this foundational experience, by designing a clinical study of MHT in the treatment of nonlesional temporal lobe epilepsy. One of the main drawbacks of the present work stems from the different physical attributes of formalin-fixed human cadaveric brains compared with a living brain; this imposes problems such as the need of larger neocortical resection and different tissue resistance to the transector penetration. Another limitation is the use of different navigation system that will be routinely used (MRI-based navigation with implemented planned trajectories of transections) were the brain shift should be corrected with the 3D ultrasound navigation.

Conclusion

This anatomical study on cadaveric brains proves the possibility to transect at least 73% of cross-section of the hippocampus perpendicular to the long axis with the aid of real-time ultrasound visualization. Modified instruments for this procedure were designed.

Conflict of Interest
None declared.

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