A novel mesial temporal stereotactic coordinate system

Kai J. Miller, MD, PhD,1 Casey H. Halpern, MD,1 Mark F. Sedrak, MD,1,2 John A. Duncan III, MD, PhD,2 and Gerald A. Grant, MD1

1Department of Neurosurgery, Stanford University, Stanford; and 2Department of Neurosurgery, Kaiser Permanente, Redwood City, California

OBJECTIVE  Stereotactic laser ablation and neurostimulator placement represent an evolution in staged surgical intervention for epilepsy. As this practice evolves, optimal targeting will require standardized outcome measures that compare electrode lead or laser source with postprocedural changes in seizure frequency. The authors propose and present a novel stereotactic coordinate system based on mesial temporal anatomical landmarks to facilitate the planning and delineation of outcomes based on extent of ablation or region of stimulation within mesial temporal structures.

METHODS  The body of the hippocampus contains a natural axis, approximated by the interface of cornu ammonis area 4 and the dentate gyrus. The uncal recess of the lateral ventricle acts as a landmark to characterize the anterior-posterior extent of this axis. Several volumetric rotations are quantified for alignment with the mesial temporal coordinate system. First, the brain volume is rotated to align with standard anterior commissure–posterior commissure (AC-PC) space. Then, it is rotated through the axial and sagittal angles that the hippocampal axis makes with the AC-PC line.

RESULTS  Using this coordinate system, customized MATLAB software was developed to allow for intuitive standardization of targeting and interpretation. The angle between the AC-PC line and the hippocampal axis was found to be approximately 20°–30° when viewed sagittally and approximately 5°–10° when viewed axially. Implanted electrodes can then be identified from CT in this space, and laser tip position and burn geometry can be calculated based on the intraoperative and postoperative MRI.

CONCLUSIONS  With the advent of stereotactic surgery for mesial temporal targets, a mesial temporal stereotactic system is introduced that may facilitate operative planning, improve surgical outcomes, and standardize outcome assessment.

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Epilepsy is a disease of abnormal electrical signal initiation and propagation throughout the brain, affecting nearly 1% of the American population. About 33% of epileptic patients are resistant to medication (having failed 2 or more appropriately dosed antiepileptic drugs), requiring surgical intervention in an attempt to control seizure frequency and severity. Temporal lobe epilepsy is the most common form of localized (focal or partial) epilepsy, and surgical intervention provides superior outcomes compared with prolonged medical therapy. However, temporal lobectomy and selective amygdalohippocampectomy for resective therapy are not without side effects, and are associated with naming difficulty, decrease in verbal memory, and (rarely) amnesia. In this context, 2 new stereotactic interventions have emerged in an effort to preserve cognitive function, while still preserving seizure freedom or reduction: MR-guided laser thermoa blation, and electrical stimulation (Fig. 1). Stereotactic laser ablation of the amygdalohippocampal complex and adjacent structures (stereotactic laser amygdalohippocampotomy [SLAH]) is performed by cannulated placement.
of a fiber-optic filament within a target brain region. The region is then heated under direct visualization, using real-time MR thermography, stopping when the desired volume of brain has been heated beyond a set threshold. SLAH has been found to provide seizure control that approaches that of open temporal lobectomy or selective amygdalohippocampectomy, while sparing object recognition and naming function. Patients with epileptic foci localized to the mesial temporal lobe are sometimes excluded from SLAH or resection in the case of bilateral disease, or if they have verbal decline or global memory deficit during selective amytal injection (the Wada test). For these patients, responsive or tonic electrical stimulation of the seizure focus via stereotactically placed depth electrodes can provide a reduction in seizure frequency and severity.

Stereotactic targeting for these approaches is evolving, although it is currently prescribed for general anatomical structures rather than a landmark-based coordinate system. The present standard for directly targeting the amygdalohippocampal complex for SLAH is defined by passing the filament through the long axis of the hippocampal body, traversing the pes hippocampi, and extending into the amygdala anteriorly; the goal for the treatment region using this standard is a tubular thermal lesion, extending (in cylindrical form) along a single axis from the amygdala extending posteriorly through the hippocampus to the transverse level of the lateral mesencephalic sulcus. Results have been quantified as percentage of amygdalohippocampal complex treated (e.g., 60%), rather than the location treated. For stimulation of the hippocampus, there are no established standards.

We believe that outcomes of these procedures may improve by adoption of a stereotactic coordinate system that is based on landmarks of the mesial temporal lobe. In this paper we propose one such system, and have created an open-source, freely available software package to test it. We believe that there is a need for anatomically based retrospective analysis in a coordinate-based system such as this one, particularly for cases of “nonlesional” mesial temporal epilepsy (e.g., no sclerosis, dysplasia). This will be relevant for a more complete understanding of proper loci for stimulation, as well as which regions are optimal for laser ablation with minimal neuropsychiatric side effects. If clear indications can be found, then this coordinate system could be used as a guide for surgical planning in much the same way as the anterior commissure–posterior commissure (AC-PC) system is currently used for structures surrounding the third ventricle.

Methods

The following is a description of the procedure for obtaining coordinates in the mesial temporal stereotactic coordinate system in a series of steps.

Identify AC-PC Coordinate Space

We begin by determining the landmarks necessary to transform to AC-PC space. The AC-PC line is identified in the standard fashion. First, the AC and PC are identified on the MR image. Then several midline points are identified. A rotation matrix is calculated to align the structural MRI with AC-PC coordinate space.

Identify Hippocampal Landmarks

We then identify hippocampal structures. The body of the hippocampus provides a natural, intuitive axis that can be identified on different imaging modalities (Fig. 2). This is approximated by the superolateral margin of the interface of the cornu ammonis area 4 (CA4) and the dentate gyrus, from the interpeduncular cistern to the superior colliculus. This is easily identified on coronal sections. Angles between the AC-PC line and the hippocampal axis from axial (θ) and sagittal (ψ) views are then calculated explicitly (Fig. 3). The uncal recess of the lateral ventricle (Fig. 4) is an ideal anterior-posterior landmark: it is robust (easily visible on both T1- and T2-weighted axial MRI), and its position is relatively conserved with both atrophy and hydrocephalus. It marks the division between the anterior extent of the hippocampal head and the posterior aspect of the overlying amygdala. The measurements illustrated in Figs. 2–4 were performed on 18 patients with epilepsy (range 23–61 years old; 10 women) whose clinical data had been approved for use by the IRBs of
the University of Washington (12 random, anonymized patients with epilepsy whose imaging is easily accessible and available [https://purl.stanford.edu/zk881ps0522]) and Kaiser Permanente (6 patients who underwent bilateral responsive neurostimulator [RNS] placement). Patients gave appropriate consent according to IRB directives.

FIG. 2. Hippocampal axis. The body of the hippocampus contains a natural, intuitive axis. This is approximated by the interface of CA4 and the dentate gyrus, from the interpeduncular cistern to the superior colliculus. A: The region of the hippocampus lies within the green oval. The hippocampal axis is noted by a green dot. Modified from Gray’s Anatomy.15 B: This histological preparation of the hippocampus illustrates the target for the hippocampal axis (green circle) at the lateral CA4 subfield where it interfaces with the dentate gyrus. Modified from Mueller SG, Weiner MW: Selective effect of age, Apo e4, and Alzheimer’s disease on hippocampal subfields. Hippocampus 19:558–564, 2009. Published with permission from John Wiley & Sons. C: Approximate cross sections of D–F. D–F: Pseudocoronal cross sections showing the target of the hippocampal axis with green circles on T1- (upper) and T2-weighted (lower) MRI. Figure is available in color online only.

FIG. 3. Angles defined by the hippocampal axis. A: The angle between the AC-PC line and the hippocampal axis when viewed sagittally (\(\phi\)) is typically approximately 20°–30° (mean 25° ± 6°), as shown by an angular histogram of 18 epileptic patients with left and right hippocampi combined. B: The angle between a parasagittal line (parallel to the AC-PC) and the hippocampal axis when viewed axially (\(\theta\)) is approximately 5°–10° (mean 3° ± 9°, significantly different from 0°, \(p = 0.003\) by resampling), as shown by the angular histogram of 12 epileptic patients with left and right hippocampi combined (after reflection of left hippocampi to right). There was no difference in \(\phi\) (\(p = 0.587\)) or \(\theta\) (\(p = 0.852\)) between left and right hippocampi (after reflecting sign of \(\theta\) for left hippocampi).
Perform Transformation to Hippocampal Stereotaxic Space

There are several volumetric rotations necessary for alignment with the mesial temporal coordinate system (Fig. 5). First, the rotations necessary to align the native MRI with the standard AC-PC space are calculated. Next, the rotations required to rotate the AC-PC line into the hippocampal axis are calculated, first by rotating from an axial perspective through the angle $q$, and then by rotating through the angle $j'$ from a pseudosagittal view. Note that this view will deviate slightly from a true sagittal view, and $j'$ is a corrected angle from $j$, because of the preceding axial ($q$) rotation. Note that only 1 equivalent rotation and reslicing of the MRI volume need be performed, whose rotation matrix is the multiplicative product of the individual rotation matrices. Following rotation, the volume is translated to have the coordinate system origin along the hippocampal axis, with anterior-posterior origin at the uncal recess.

Practical Implementation With Customized Software

All pre- and postprocedural MR and CT imaging is converted from standard DICOM (.dcm) directory to NIfTI (.nii) format. Then, the anterior/posterior commissures, several distant midline points, several hippocampal axis points, and the uncal recess are selected manually from a preoperative anatomical T1- or T2-weighted image. This image is then resliced into 1 mm³ mesial temporal (or AC-PC, if desired) stereotactic space using an affine transformation (https://www.mathworks.com/matlabcentral/fileexchange/8797-tools-for-nifti-and-analyze-image). All other images are then coregistered and resliced into this image using normalized mutual information (Fig. 6). Pre- and postprocedural images are visualized simultaneously, and electrode positions, fiber optic trajectories, or burn regions are selected and exported into data files so that they can later be used for averaging across patients. A customized graphical user interface package (the “Hippotaxy” MATLAB-based code) allows for the automation of this process, and is available along with an instructional guide and video illustrations (http://purl.stanford.edu/pn316qg0195). The freely available MATLAB-based SPM12 software is used for DICOM to NIfTI conversion and coregistration/reslicing (http://www.fil.ion.ucl.ac.uk/spm/software/).

Illustration of Mesial Temporal Stereotaxy in a Small Cohort

To provide a small practical demonstration of how mesial temporal stereotaxy can be useful, we quantified electrode placement in 6 patients who underwent bilateral 4-contact RNS lead placements for epilepsy. The Kaiser Permanente IRB approved all patient data for retrospective analysis, and consent was obtained from patients accordingly. For these 12 leads, electrode positions in AC-PC and mesial temporal stereotactic space were measured with the Hippotaxy software. Comparisons of electrode spatial spread were made by performing a principal component decomposition to determine the principal axes of the distributions. The eigenvalue associated with each of these principal axes is used as the measure of spatial spread along the associated axis (Fig. 7). For each permutation in the
resampling analysis illustrated in Fig. 7E, the same random subset of two-thirds of electrodes was picked in the AC-PC and mesial temporal stereotactic coordinate system, and the principal component decomposition (with associated eigenvalues) was performed on the subset. One thousand resampling permutations were performed.

**Results**

Using the customized software we call Hippotaxy, the midline point and the anterior/posterior commissures were easily identified on the axial and coronal MR images (Fig. 2). Similarly, the body of the hippocampus was easily identified, even in the case of mesial temporal sclerosis, on both the right and left sides. As noted in Fig. 3, the average angle between the AC-PC line and the hippocampal axis when viewed sagittally (\( \theta \)) was \( 25° \pm 6° \) (18 patients, left and right hippocampi combined). The angle between a parasagittal line (parallel to the AC-PC) and the hippocampal axis when viewed axially (\( \phi \)) was \( 3° \pm 9° \) laterally rotated (18 patients, with left hippocampi reflected to the right, significantly different from \( 0° \); \( p = 0.003 \) by permutation resampling). There was no difference in \( \phi \) (\( p = 0.587 \)) or \( \theta \) (\( p = 0.652 \)) between left and right hippocampi (after reflecting left hippocampi to the right). As shown in Fig. 4, the uncal recess was easily identifiable. The transformation to mesial temporal stereotactic space was robust and reliably reveals the long axis of the hippocampus (Figs. 5 and 6). Anatomical points and volumes are identified and exported to MATLAB data files and raw text files for later averaging.

To illustrate why this mesial temporal stereotactic space is useful, we characterized a small cohort of 6 consecutive bilateral RNS placements for bitemporal epilepsy. Because the placements were all performed by the same experienced surgeons (J.A.D. and M.F.S. jointly) for the same indication, the planning and surgical procedure is as optimally reproducible as we might be able to expect, based on direct targeting via visual inspection of the MRI. Therefore, we can use this for a simple comparison of our proposed mesial temporal stereotactic space versus the AC-PC stereotactic space, which is the current standard for stereotactic targeting and assessment. As shown in Fig. 7, the spread in distribution is significantly more compact for the case of mesial temporal stereotaxy (\( p < 0.001 \), \( p < 0.001 \), and \( p = 0.021 \) for principal dimensions 1–3, respectively). In Fig. 8, we show simple histograms of the electrode placements in mesial temporal stereotactic space.

**Discussion**

Early surgical intervention for mesial temporal lobe epilepsy benefits disease progression over medical therapy alone,\(^1\) and these stereotactic procedures minimize the negative sequelae.\(^4\) Laser ablation of the mesial temporal lobe has demonstrated efficacy in both adult and pediatric patients.\(^3\) Laser ablation and stimulation are each now used as either primary therapies or adjuvant therapies following surgery for lateralized temporal onset of seizures in patients with medically refractory epilepsy. In the case of bitemporal epilepsy, one could ablate the nondominant mesial temporal lobe and place an RNS on the dominant side.

Occipital approaches to the hippocampus and adja-
FIG. 6. The Hippotaxy software is a pair of custom programs that are freely available MATLAB-based graphical user interfaces (GUIs). A: Illustration of parsing a T1-weighted MR image, selected along the hippocampal axis. This GUI is used for browsing MR and CT images, selecting mesial temporal landmarks, coregistering images, and obtaining resliced images in both AC-PC and mesial temporal stereotactic space. B: A second GUI is used for simultaneous viewing of coregistered images (pre-/post-procedural on the left/right, respectively). It can be used for selecting electrode locations and burn regions viewed in this mesial temporal stereotactic space (or AC-PC if desired). Selected locations and regions can be exported to a text file or MATLAB data file, where their values in this mesial temporal stereotactic space can be aggregated across many patients. Figure is available in color online only.
cent structures evolved from depth electrode approaches for electrophysiological recording in seizure monitoring. These approaches, pioneered by the Spencers, \textsuperscript{24–26} generally correspond to our “principal axis” to maximize the number of recording leads in the hippocampus. This axis is also commonly referred to as the “long axis of the hippocampus.” \textsuperscript{32} The “hippocampal axial plane” described by Beaurain and colleagues\textsuperscript{1} shares some similarity to our coordinate system, but is parasagittal, and therefore oblique to the long axis of the hippocampus. It should be noted that recent series with laser ablation do not aim along the principal axis, but rather favor a steeper, lateral-to-medial approach. \textsuperscript{32} This allows for more extensive ablation of the uncus, at the expense of posterior portions of the hippocampal body.

The choice of coordinate system is not meant to align with the optimal trajectory, but to be robust with respect to hippocampal anatomy across patients. Of important note, the axes of this coordinate system, particularly the long/principal axis of the hippocampus, need not have any relation to optimal ablation or electrode placement loci. We are as yet not sure what the best regional structures within the mesial temporal lobe will be, and our hope is that optimal trajectories will emerge from a probabilistic map after anatomical analysis of a large cohort is compared with seizure semiology and postoperative outcome. It may be that these optimal trajectories correspond to transverse (transtemporal) or oblique approaches. This system will allow comparison of targeting volume with seizure reduction and postoperative deficit. If useful, this coordinate system and these trajectories could be easily adapted and integrated into existing commercial stereotactic guidance platforms, as well as robotic targeting systems.\textsuperscript{14}

The hippocampus has widespread and diverse cortical projections. It may be that slightly different semiology implies that a different mesial temporal structure is generating or propagating the seizure. This mesial temporal coordinate system approach could be used to develop an electrophysiological map of the hippocampus. With careful analysis, we might actually begin to be able to understand

FIG. 7. A comparison of AC-PC space and mesial temporal stereotactic space in a small cohort. Six consecutive bilateral posterior-approach RNS leads were implanted (12 four-electrode leads, 48 total electrodes), and here we ask: Is there a way of representing this surgeon’s electrode placement that captures his direct targeting strategy? A and B: Two examples of electrode placement are shown alongside the outlined hippocampus. C: The overlaid electrodes/hippocampi from A and B are shown. The spread in data along the principal dimensions (Dim) of the combined distributions of electrodes is indicated beneath. D: Similar to panel C, but after the electrodes have been transformed to mesial temporal stereotactic space, showing how the data spread changes. The spread in data along all 3 principal dimensions (in descending order) was smaller in the mesial temporal stereotactic space than in the AC-PC space. E: Permutation testing was performed by randomly selecting two-thirds of the data (32 electrodes) and recalculating principal dimensions and spread along each dimension 1000 times, showing that electrode positions significantly favor the mesial temporal stereotactic space (p values of < 0.001, < 0.001, and 0.021 for dimensions 1–3, respectively). Because the surgeon was directly targeting mesial temporal structures along the length of the hippocampus, use of mesial temporal stereotactic space clusters the full complement of electrodes more tightly than does use of AC-PC space. Figure is available in color online only.
clustered “morphologies”—combined semiological and anatomical findings—that implicate specific subregions of the amygdalohippocampal complex. These subregions might act as primary generators of seizures, a conduit for focus elsewhere, or a kindled secondary focus.

In collaboration with colleagues at other institutions, we are currently validating this hippocampal stereotaxic space in a cohort of patients in a retrospective fashion to better characterize the extent of laser ablation as well as placement of depth electrodes for neurostimulation. We anticipate that this will be the first step, but that hippocampal stereotactic approaches will evolve as stereotactic surgery for epilepsy becomes more widely adopted. In addition to evaluation of efficacy and cognitive sequelae following stereotaxic surgery, there should also be comparison with preoperative anatomic variation and seizure semiology. Standardized targeting in this coordinate system may be developed for more precise intervention, and also to link anatomy to specific seizure semiology (rather than just general localization to the mesial temporal lobe). There may in fact be different hippocampal or amygdalar targets based on the seizure semiology or electroencephalography, or for variations in sclerosis, which are only revealed by systematic analysis of many patients in a common space. In the case of nonlesional mesial temporal epilepsy (e.g., no sclerosis, dysplasia), there may be different focal targets for stimulation or lesioning, depending on the semiology.

Stereotactic placement of stimulating electrodes and laser filaments has emerged as an important component of epilepsy therapy. Optimal stereotactic targeting will require standardized outcome measures that compare electrode lead or laser source with postprocedural changes in seizure frequency. However, there is no standardized approach for how this should be performed for the hippocampus and surrounding structures. We therefore describe a referential stereotactic coordinate system based on mesial temporal anatomical landmarks, taking advantage of a natural axis through the body of the hippocampus and a reliable anchor point provided by the uncal recess of the lateral ventricle. This coordinate system may facilitate operative planning, improve surgical outcomes, and standardize outcome assessment.

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The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Miller. Acquisition of data: all authors. Analysis and interpretation of data: Miller. Drafting the article: Miller. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miller. Statistical analysis: Miller.

Correspondence

Kai J. Miller: Stanford University, Stanford, CA. kai.miller@stanford.edu.