Volumetric Magnetic Resonance Imaging

Clinical Applications and Contributions to the Understanding of Temporal Lobe Epilepsy

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In recent years, magnetic resonance imaging–based volumetric measurements of the amygdala and hippocampus have proved useful in the diagnosis and treatment of patients with temporal lobe epilepsy. This imaging modality allows amygdaloid and hippocampal volumes to be correlated with neurophysiological, neuropathological, and neuropsychological findings, surgical outcome, and clinical findings. We evaluated the technical and anatomical aspects underlying the successful use of the modality that were reported in previous studies. We also evaluated issues such as the sensitivity and specificity of volumetric magnetic resonance imaging, its use in bilateral temporal lobe epilepsy, and the debate concerning the sensitivity of qualitative visual analysis vs quantitative volumetric analysis of magnetic resonance images. Volumetric magnetic resonance imaging, when used in conjunction with video electroencephalographic monitoring, neuropsychological studies, and other neuroimaging studies, will enable patients with temporal lobe epilepsy to be treated in an appropriate, efficient, and cost-effective manner. *Arch Neurol. 1997;54:1521-1531*

Magnetic resonance (MR) imaging–based volumetric measurements of the amygdala and hippocampus provide useful in vivo neuroanatomical information in a number of clinical settings, including temporal lobe epilepsy, amnesia, schizophrenia, and Alzheimer disease. In temporal lobe epilepsy, volumetric MR imaging allows the correlation of preoperative and postoperative amygdaloid and hippocampal volumes with neurophysiological, neuropathological, and neuropsychological findings, surgical outcome, and clinical findings. The addition of amygdaloid volume measurements to those of the hippocampus may allow assessment of the relative contribution of each of these structures to epileptogenesis and memory function. Postoperative quantification of the amount of amygdaloid and hippocampal resection may yield a better understanding of which structures need to be removed and in what volume. Amygdaloid and hippocampal volume measurements may also be helpful in providing supplementary information in patients with bilateral temporal ictal onsets when used in conjunction with electroencephalograms (EEGs) and other localizing studies. Volumetric MR imaging, when used in conjunction with other neuroimaging studies, will reduce the number of patients who require prolonged, invasive, and expensive video EEG monitoring with intracranial electrodes. This should allow more patients to be treated in an appropriate, efficient, and cost-effective manner by means of noninvasive video EEG monitoring coupled with neuropsychological studies and noninvasive imaging techniques.

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TECHNICAL ASPECTS

Histologically, the hallmarks of hippocampal sclerosis (HS) are cell loss and astrogliosis (sclerosis) of the hippocampus and related medial temporal lobe limbic areas.[1] The 2 principal MR imaging findings in histologically proved cases of HS are hippocampal atrophy and MR imaging signal changes indicative of increased tissue free water.[2-6] Both of these MR imaging properties can be quantified.[3,7] Hippocampal volu-

metry is a direct measure of the hippocampal atrophy associated with HS. Several studies have demonstrated a close correlation between histologically determined cell loss and atrophy determined through hippocampal volumetric measurements.[8-15] Magnetic resonance imaging–based hippocampal volumetric measurements therefore may be considered a surrogate for pathologic identification not only of the presence, but also of the relative severity, of HS in *both* hippocampi.

To maximize the precision and reproducibility of MR imaging–based hippocampal volume measures, the technical variables used when the images themselves are acquired should reflect the following guidelines[16]: (1) Spatial resolution should be maximized. In practical terms this means that the imaging sections (or slices) should be made as thin as possible (while preserving signal-to-noise ratio) to avoid volume averaging artifacts in the direction of voxel anisotropy. (2) To optimally display hippocampal boundaries, the contrast-to-noise ratios between gray matter, white matter, and cerebrospinal fluid should be high enough to permit reliable discrimination of hippocampal boundaries. (3) The image acquisition time should be short enough (<10 minutes) that high-quality images free of motion artifact may be acquired in the vast majority of patients being screened.

The preceding criteria lead to 2 logical choices for the optimum type of MR imaging sequence to be used for subsequent volume measurements. The most commonly used approach is a 3-dimensional volumetric pulse sequence. At our institutions, a 3-dimensional volume gradient echo pulse sequence acquired in an oblique plane perpendicular to the main axis of the left hippocampal formation is used.[16] It is radiofrequency spoiled, which largely obviates the problem of cerebrospinal fluid pulsation artifacts. A rectangular field of view is used to reduce total imaging time to under 10 minutes. One hundred twenty-four partitions are acquired at 1.6 mm per partition. This results in an image data set that not only is useful for hippocampal volume measurements but provides whole-head anatomical coverage for routine diagnostic purposes. Although acquisition of a partial echo (so-called fractional echo sampling) will reduce the total imaging time, we have found that fractional echo sampling greatly increases the magnitude of susceptibility artifacts at the basal temporal–petrous bone interface in some patients, and, to avoid this, we use a full echo sampling scheme. The second type of image sequence that has been successfully used in recent years for hippocampal volume measurements is 2-dimensional fast spin echo with thin (2-mm) slices.[12,17,18] A potentially attractive alternative to both of these approaches is a 3-dimensional fast spin echo approach. Clinically practical 3-dimensional fast spin echo imaging will be enabled by installation of high-performance gradient sets that have recently been made commercially available by the major MR imaging equipment vendors and are being installed at a number of sites.

An alternative to image acquisition in the coronal (or oblique coronal) plane that has been used by some authors is image acquisition in the sagittal plane.[19] The disadvantage of sagittal image acquisition is that to visually compare the hippocampi for the presence of relative side-to-side atrophy for diagnostic purposes, the images must be secondarily reformatted in the coronal plane, and thus the native or raw MR images as they are acquired are not suitable for the clinical visual evaluation of hippocampal atrophy. Some authors have actually outlined the hippocampus for volumetric determination in the sagittal plane. While this approach works well for most of the hippocampal borders, portions of the hippocampal border are optimally displayed only in the coronal plane, not the sagittal plane, particularly the medial subicular–parahippocampal boundary, the medial boundary between the hippocampal head and the amygdala–ambient gyrus, and the posterior border of the hippocampus.[20]

After the image dataset has been acquired, it must be processed to produce volume measurement information. This step requires great attention to detail to produce precise and accurate hippocampal and amygdaloid volume measurements. This is generally done by transferring the MR images to a computer workstation and manually tracing hippocampal and amygdaloid borders on serial planimetric slices with a manual interactive device. Manual tracing of hippocampal and amygdaloid borders creates a volume of interest. The voxels inside the volume of interest are then automatically counted by the computer and multiplied by the number of cubic millimeters per image voxel to generate hippocampal and amygdaloid volumes in cubic millimeters. Discrepancies between the way different software programs handle the counting of border pixels in a traced volume of interest are a likely cause of the discrepancies among various sites for the "normal" absolute volume of the right and left hippocampi and amygdalae in normal subjects. The second likely source for interinstitutional variability in reported "normal" hippocampal and amygdaloid volumes is the neuroanatomical boundary criteria used to define hippocampal borders.[14-16,20-27] Rigorous standardized criteria that have a solid neuroanatomical basis must be followed when the borders of the amygdala and hippocampus are traced, to ensure precise and reproducible volume measurements.[20,28]

INTERPRETATION

Magnetic resonance imaging–based volume measurements of the right and left hippocampus (or amygdala) may be interpreted in 2 ways (relative or absolute). To date, the relative approach, in which the right and left hippocampi in a given patient are compared by taking either a right-to-left hippocampal ratio or the difference between the 2 sides, has been used more commonly. Evaluating hippocampal volume in absolute terms is more complex because a number of variables other than the variable of interest—the presence and severity of HS—affect hippocampal volume in any given subject.

Variables that have been shown to affect hippocampal volume in normal individuals are head size, age, sex, and hemisphere.[24,29,30] As a negative phenomenon, atrophy does not lend itself to straightforward traditional counting methods but must be inferred by comparison with normative data on appropriately matched control populations. Ideally, therefore, atrophy of the right or left hippocampus (or both) in any individual would be established by

comparing those values with normative percentiles in an age- and sex-matched control population for that hemisphere, and after adjustment for head size. Hippocampal atrophy in any given patient as a marker of HS would then be expressed in terms of the percentile of adjusted volume in normal subjects. As a rule, studies in epilepsy in which hippocampal volume has been analyzed in absolute terms have not taken into account age effects, because age-related effects on hippocampal volume are found primarily in the very young, because of growth and development, and in older individuals, because of age-related atrophy.[24,30] Hemispheric effects have been nonuniformly reported in the literature, with some studies finding the right hippocampus to be larger in normal subjects and other studies finding no right-left difference.[20-27] These differences in the literature in the reported normal volume of the right relative to the left hippocampus may be caused in large part by the use of different boundary criteria; nonetheless, a clear consensus does not exist as to whether a normal right-left difference exists in hippocampal volume. The effect of sex is small in comparison with that of head size. Therefore, the few studies that used absolute volumetric quantitation in epilepsy have adjusted hippocampal volume only by intracranial volume. This adjustment can take several forms. The 2 most popular are (1) dividing hippocampal volume by total intracranial volume to create a ratio and (2) a covariance approach.[24,29,30-34] One method of "normalization" by total intracranial volume is as follows: (1) Obtain the mean total intracranial volume (TIV) of the normal control group. (2) "Normalize" the volume of each of the structures measured (eg, hippocampal formation [HF] or amygdala [AM]) for individual variation in head size, using the formula "Normalized" HF (or AM) Volume=[RxHF (or AM) Volume], where R is the mean TIV of the controls divided by the patient's TIV.

In addition to validating the accuracy and reproducibility of volume measurements, each center must also establish the range of normal values present in their patient and control populations. A number of factors enter into the absolute values obtained at each institution, as mentioned above, and therefore discrepancies between institutions are to be expected. This requires that each institution create its own normal database.[14-16,20-27,31]

ANATOMICAL ASPECTS

The person performing the volumetric measurements of the amygdala and hippocampus must have a detailed knowledge of the anatomy of the medial temporal region if these measurements are to be accurate and reliable. In addition, the structures must be measured consistently according to a predetermined and standardized protocol. Such protocols have been published in detail.[16,20] When the boundaries of the hippocampus and amygdala are measured by a knowledgeable investigator according to a predetermined and standardized protocol, the accuracy and reproducibility of the measurements are high.[14-16,20-23] The following protocol (from our original article)[20] represents our recommendation for measuring amygdaloid and hippocampal volumes.[16,20,21,23]

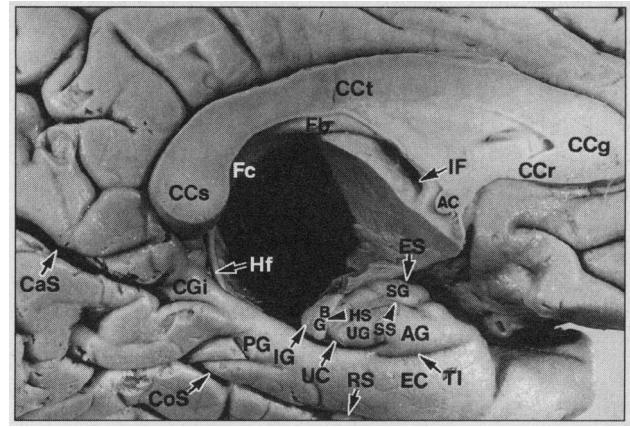

Figure 1. *Medial view of the left cerebral hemisphere showing surface anatomy of the medial temporal lobe (adapted from Watson et al[20]). AC indicates anterior commissure; AG, ambient gyrus; BG, band (limbus) of Giacomini; CaS, calcarine sulcus; CCg, corpus callosum, genu; CCr, corpus callosum, rostrum; CCs, corpus callosum, splenium; CCt, corpus callosum, trunk; CGi, isthmus of cingulate gyrus; CoS, collateral sulcus; EC, entorhinal cortex; ES, endorhinal sulcus; Fb, fornix, body; Fc, fornix, crus; Hf, fibria of hippocampus; HS, hippocampal sulcus; IF, interventricular foramen; IG, intralimbic gyrus; PG, parahippocampal gyrus; RS, rhinal sulcus; SG, semilunar gyrus; SS, semiannular (amygdaloid) sulcus; TI, tentorial indentation; UC, uncal cleft; and UG, uncinate gyrus.*

Amygdaloid Volume

The amygdala is an ovoid mass of gray matter situated in the superomedial portion of the temporal lobe, partly above the tip of the inferior horn of the lateral ventricle. It occupies the superior part of the anterior segment of the uncus and partially overlies the head of the hippocampus, being separated from that structure by the uncal recess of the inferior horn of the lateral ventricle. On the superomedial surface of the uncus, the amygdala forms a distinct protrusion, the semilunar gyrus, which corresponds to the cortical amygdaloid nucleus. It is separated from the ambient gyrus by the semiannular or amygdaloid sulcus, which forms the boundary between the amygdala and the entorhinal cortex. The latter extends into the ambient gyrus and forms most of its surface. The amygdala is separated from the substantia innominata by a deep fold, the endorhinal sulcus, which is lined on the amygdaloid side by the medial nucleus of the amygdala. The superior rim of the ambient gyrus, lying in the fundus of the semiannular sulcus, is related to the so-called corticoamygdaloid transition area, which probably represents periamygdaloid cortex.[35] The medial surface of the ambient gyrus often shows a marked indentation, the tentorial indentation (also sometimes called the uncal notch[28] or the intrarhinal sulcus[36]), produced by the free edge of the tentorium cerebelli (**Figure 1**).

The anterior end of the amygdala is arbitrarily and consistently measured on the MR imaging section at the level of the closure of the lateral sulcus to form the endorhinal sulcus. Although we recognize that this procedure potentially excludes part of the anterior amygdaloid area, we believe that this region is too difficult to visualize reliably on MR imaging and might consist of other structures, such as the anterior-inferior extent of the claustrum and the endopyriform nucleus. The medial border of the amygdala is covered by part of the entorhinal cortex, which forms the surface of the ambient

gyrus in this region. The entorhinal cortex inferior to the tentorial indentation is excluded from the amygdaloid measurement. If the tentorial indentation is poorly defined or not visible in the anterior amygdaloid region, the line of demarcation between the amygdala and the adjacent entorhinal cortex that occupies the ambient gyrus is defined by a line drawn in direct continuation with the inferior and medial border of the amygdala within the substance of the temporal lobe. By proceeding in this manner, a small amount of the superior extent of the entorhinal cortex is included in the amygdaloid volume, as is the case when the tentorial indentation is used as the landmark. The inferior and lateral borders of the amygdala are formed by the inferior horn of the lateral ventricle or white matter (**Figure 2**). To define the superior border of the amygdala, we draw a straight line laterally from the endorhinal sulcus to the fundus of the inferior portion of the circular sulcus of the insula. More posteriorly, the optic tract is used as a guide to the lateral extension of the crural cistern into the transverse cerebral fissure. This locates the medial aspect of the posterior amygdala and is used as the point of departure for defining the medial and superior borders of the structure posteriorly. To define the superior border of the amygdala at this level, a straight line is drawn laterally from the superolateral aspect of the optic tract to the fundus of the inferior portion of the circular sulcus of the insula (**Figure 3**).

This method of defining the superior border of the amygdala is arbitrary and undoubtedly excludes small amounts of the medial and central nuclei. However, it should prevent such structures as the substantia innominata, inferior portion of the putamen, and inferior portion of the claustrum from being included in the amygdaloid measurement. At its posterior end, the amygdala occupies the medial half of the roof of the inferior horn of the lateral ventricle, and care must be taken to exclude the tail of the caudate nucleus, the overlying globus pallidus and putamen, and the lateral geniculate body (**Figure 4**). In cases in which the border of the putamen cannot be clearly defined, only the medial half of the structures in the roof should be included in the amygdaloid volume at this level.

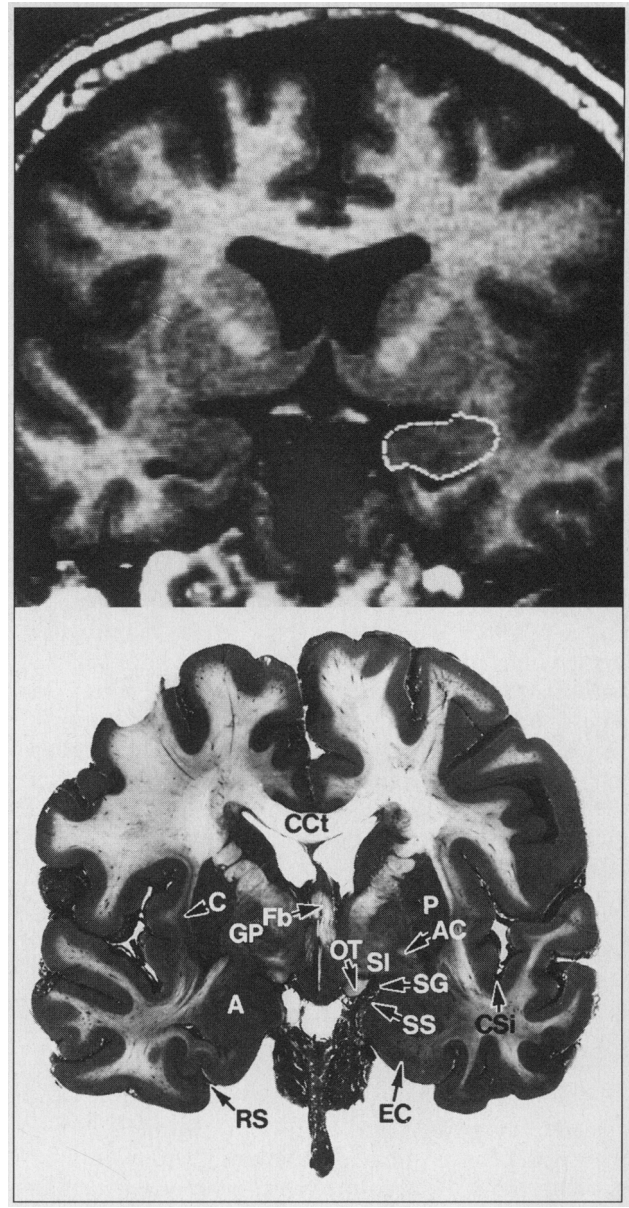

Figure 2. *Angled coronal sections of the cerebral hemispheres passing through the anterior segment of the uncus (adapted from Watson et al[20]). Top, Magnetic resonance image with the amygdala outlined on the left. Bottom, Brain section stained with the LeMasurier modification of the Mulligan stain. A indicates amygdala; AC, anterior commissure; C, claustrum; CCt, corpus callosum, trunk; CSi, circular sulcus of insula; EC, entorhinal cortex; Fb, fornix, body; GP, globus pallidus; OT, optic tract; P, putamen; RS, rhinal sulcus; SG, semilunar gyrus; SI, substantia innominata; and SS, semiannular (amygdaloid) sulcus.*

Hippocampal Volume

The hippocampus is a complex structure consisting of an enlarged anterior part that has been called the pes, but perhaps is better termed the head of the hippocampus. This portion of the hippocampus exhibits 3 or 4 digitations and turns medially to form the posterior segment of the uncus. As it turns medially, the hippocampus and the dentate gyrus run in the roof of the uncal cleft (also sometimes called the uncal notch, the uncal sulcus,[28] and, erroneously, the hippocampal sulcus), the sulcuslike cleft that separates the uncus above from the parahippocampal gyrus below. Once the hippocampus and dentate gyrus reach the medial surface of the uncus, they turn up and form the posterior one third of the medial and superomedial surface of the uncus. Macroscopically the dentate gyrus is discernible as a narrow elevation, the band or limbus of Giacomini. This is interposed between the intralimbic gyrus, which forms the posterior pole of the uncus and corresponds to sector CA3 of the hippocampus, and the uncinate gyrus, which extends anterior to the band of Giacomini and corresponds partially to sector CA1 and the subiculum. There is no macroscopically visible border between the uncinate gyrus and the ambient gyrus. The floor of the uncal cleft is formed by the presubiculum (Figure 1). The body of the hippocampus curves around the upper midbrain and is concave medially. The anatomy in this region is much less complex. Posteriorly, the hippocampal body tapers into the tail, which turns medially just anterior to and below the splenium of the corpus callosum. The tail of the hip-

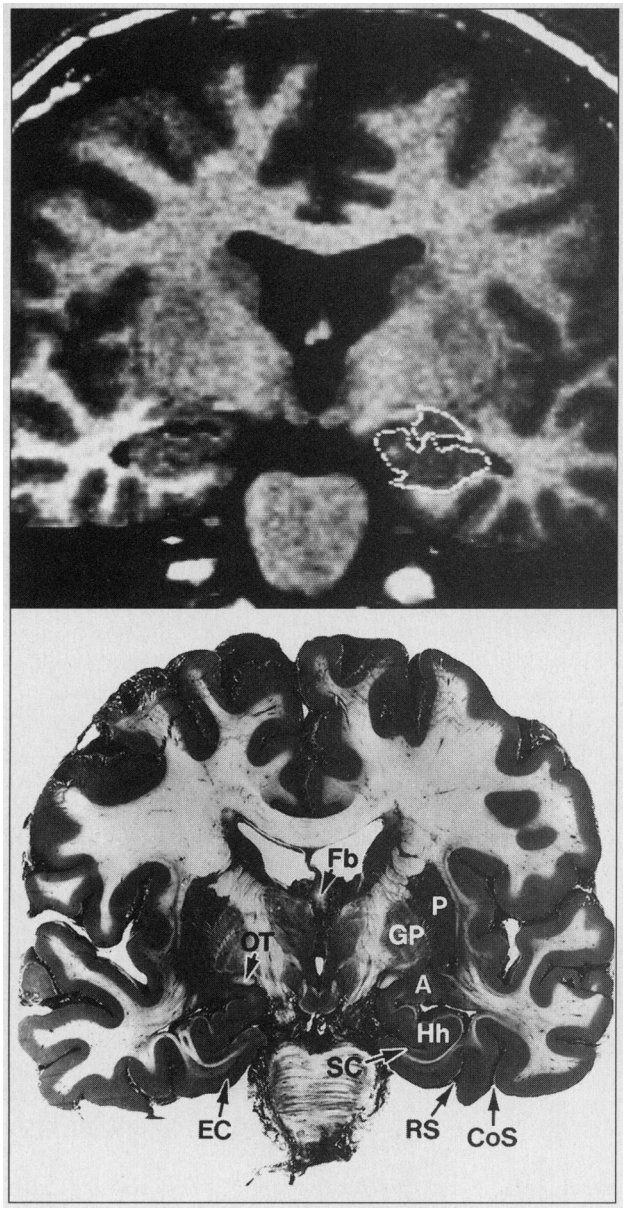

Figure 3. *Angled coronal sections of the cerebral hemispheres passing through the posterior segment of the uncus (adapted from Watson et al[20]). Top, Magnetic resonance image with the amygdala and hippocampal head outlined on the left. Bottom, Brain section. A indicates amygdala; CoS, collateral sulcus; EC, entorhinal sulcus; Fb, fornix, body; GP, globus pallidus; Hh, hippocampus, head (pes); OT, optic tract; P, putamen; RS, rhinal sulcus; and SC, subicular complex.*

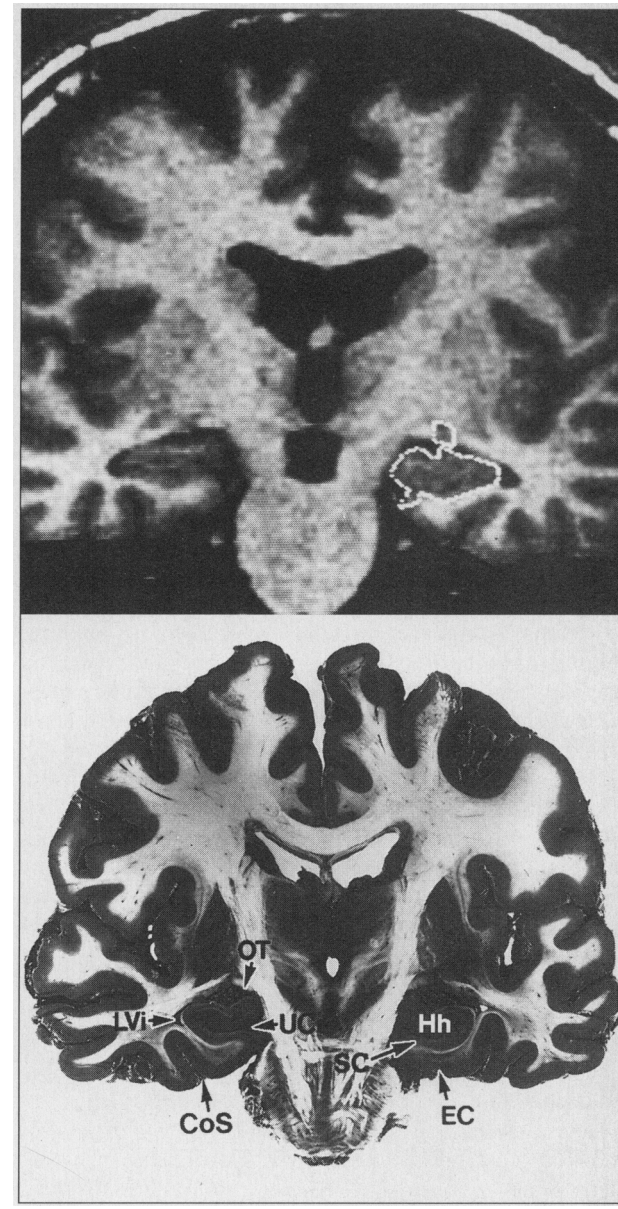

Figure 4. *Angled coronal sections of the cerebral hemispheres passing through the posterior segment of the uncus (adapted from Watson et al[20]). Top, Magnetic resonance image with posterior portion of the amygdala and posterior portion of the hippocampal head outlined on the left. Bottom, Brain section. CoS indicates collateral sulcus; EC, entorhinal sulcus; Hh, hippocampus, head (pes); LVi, lateral ventricle, inferior horn; OT, optic tract; SC, subicular complex; and UC, uncal cleft.*

pocampus gives rise to the fasciola cinerea, which ultimately passes around the corpus callosum to continue on its upper surface as the indusium griseum.

It is obviously most difficult to define the boundaries of the hippocampus in its most anterior portion, the hippocampal head. The most reliable structure separating the head of the hippocampus from the amygdala in this region is the inferior horn of the lateral ventricle. This is especially true if the ventricular cavity extends into the deep part of the uncus anterior to the head of the hippocampus, thereby forming the uncal recess of the inferior horn. However, portions of the uncal recess are often obliterated, especially medially, and the hippocampal digitations are fused to the amygdala across the ventricular cavity.[28] When this is the case, 3 guidelines are used to outline the hippocampal head and separate it from the adjacent amygdala. If an obvious semilunar gyrus is present on the surface of the uncus, a line is drawn connecting the inferior horn of the lateral ventricle to the sulcus at the inferior margin of the semilunar gyrus (ie, the semiannular or amygdaloid sulcus). It is also useful to use the alveus covering the ventricular surface of the hippocampal digitations to distinguish the hippocampus from the amygdala. As a white matter tract, the alveus has a distinctly higher signal than the adjacent gray matter on T1-weighted MR images. If neither the semiannular sulcus nor the alveus is obvious, a straight horizontal line is drawn connecting the plane of the inferior horn of the

lateral ventricle with the surface of the uncus. The inferior margin of the hippocampus is outlined to include the subicular complex and the uncal cleft. The border separating the subicular complex from the parahippocampal gyrus is defined as the angle formed by the most medial extent of those 2 structures. Unless significant atrophy is present, no attempt is made to outline the gray matter on the superior and inferior banks of the uncal cleft, as it is usually quite narrow. The gray matter of the entorhinal cortex or parahippocampal gyrus is excluded from this measurement (Figures 3 and 4).

In the hippocampal body, the delineation of the hippocampus includes the subicular complex, hippocampus proper, dentate gyrus, alveus, and fimbria. The border between the subicular complex and the parahippocampal gyrus is defined in the same manner as in the hippocampal head. Therefore, the cortex of the parahippocampal gyrus is once again excluded from the measurement (**Figure 5**).

In the hippocampal tail, measurement again includes the subicular complex, hippocampus proper, dentate gyrus, alveus, and fimbria. Excluded at this level are the crus of the fornix, isthmus of the cingulate gyrus, and parahippocampal gyrus. The most posterior section measured is the section with the crus of the fornix clearly separating from the hippocampus and its fimbria (**Figure 6**). This leaves a small segment of the tail of the hippocampus outside the measured hippocampal volume.

Since the distance from the anterior end of the hippocampus to the point of separation of the crus of the fornix from the fimbria of the hippocampus is approximately 35 to 38 mm, we estimate that the entire hippocampus except for its most posterior 2 to 4 mm is included in the volume measurement. Therefore, assuming a total anterior-posterior length of the hippocampus of approximately 40 mm,[36,37] these guidelines should result in a volume measurement of 90% to 95% of the total hippocampal formation.

CORRELATION WITH EEG

Since the initial publication on the utility of volumetric MR imaging measurements of the hippocampus in patients with temporal lobe epilepsy by Jack et al,[3] many studies have illustrated the positive correlation between the EEG lateralization of the epileptogenic region in temporal lobe epilepsy and the presence of significantly reduced hippocampal volumes.[3,31,38-45] The sensitivity and specificity of these observations varies depending on the patient population studied, but all of the studies found the 2 techniques to be complementary. In a recent study, Cendes et al[31] found that hippocampal volumes were more sensitive than amygdaloid volumes and agreed with lateralization of the epileptogenic region as defined by extracranial and intracranial EEG in 87% of cases. When both hippocampal and amygdaloid volumes were considered, however, lateralization was correct in 93% of cases. These studies indicate that volumetric measurements of the hippocampal formation and amygdala are very sensitive in lateralizing the epileptogenic region.

Recently, Gambardella et al[43] reviewed clinical and scalp EEG findings in 61 consecutive patients with temporal lobe epilepsy and atrophy of medial temporal structures and found that interictal spikes had a maximal field over the anterior temporal regions in 63% of patients with atrophy of the amygdala. In contrast, interictal spikes in patients with isolated hippocampal atrophy were never maximal anteriorly. In addition, secondarily generalized seizures and syncopal spells were correlated with anatomically extensive atrophy, particularly involving the amygdala, confirming previous observations by Cook et al.[22]

In another study, Gambardella et al[44] found that in temporal lobe epilepsy related to medial temporal atrophy, delta transients are a reliable indicator of the epileptogenic focus and presumably reflect the underlying epileptogenic process rather than just structural abnormality.

CORRELATION WITH INTRACRANIAL STEREOTAXIC DEPTH EEG

Cendes et al[32] studied a group of 31 consecutive patients with bilateral scalp EEG abnormalities who underwent intracranial EEG investigation to determine the relationship between medial temporal atrophy and intracranial ictal and interictal stereo EEG abnormalities. They found a significant correlation between the severity of stereo EEG background disturbance and the degree of medial temporal atrophy, but no significant correlation between the frequency of stereo EEG interictal spikes and the amount of medial temporal atrophy. This suggests that continuous polymorphic slow waves and decrease or loss of normal fast rhythms may reflect more accurately the epileptogenic damage in medial temporal structures than does the frequency of interictal epileptiform discharges. This study also showed that unilateral medial atrophy predicts ipsilateral medial stereo EEG seizure onset despite bitemporal extracranial EEG foci.[32]

CORRELATION WITH PATHOLOGIC FINDINGS

Several studies have correlated hippocampal volumes with pathological findings in temporal lobectomy specimens.[8-13] A strong relationship between the degree of hippocampal volume loss and the severity of HS was found in studies that used qualitative,[8,10] semiquantitative,[13] and quantitative[9,11,12] neuropathological techniques. In view of these findings, it appears that the severity of HS can be predicted preoperatively by means of hippocampal volumes and hippocampal ratios. This information should be useful in the diagnostic, therapeutic, prognostic, and research aspects of the treatment of patients with medically intractable temporal lobe epilepsy caused by HS.

CORRELATION WITH NEUROPSYCHOLOGICAL STUDIES

It is well recognized that medial temporal lobe structures such as the entorhinal cortex and the hippocampus play a critical role in declarative memory function. It is not surprising, therefore, that a relationship has been demonstrated between the severity of hippocampal atrophy, as measured by volumetric MR imaging studies,

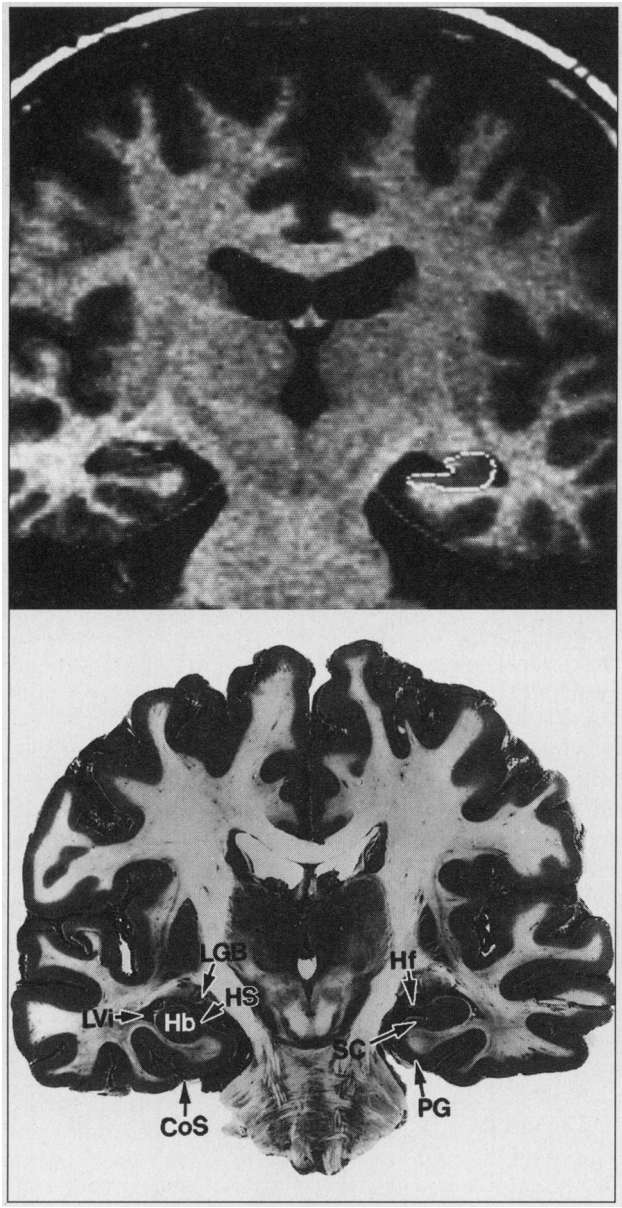

Figure 5. *Angled coronal sections of the cerebral hemispheres passing through the lateral geniculate body and the parahippocampal gyrus (adapted from Watson et al[20]). Top, Magnetic resonance image with the hippocampal body outlined on the left. Bottom, Brain section. CoS indicates collateral sulcus; Hb, hippocampus, body; Hf, fimbria of hippocampus; HS, hippocampal sulcus; LGB, lateral geniculate body; LVi, lateral ventricle, inferior horn; PG, parahippocampal gyrus; and SC, subicular complex.*

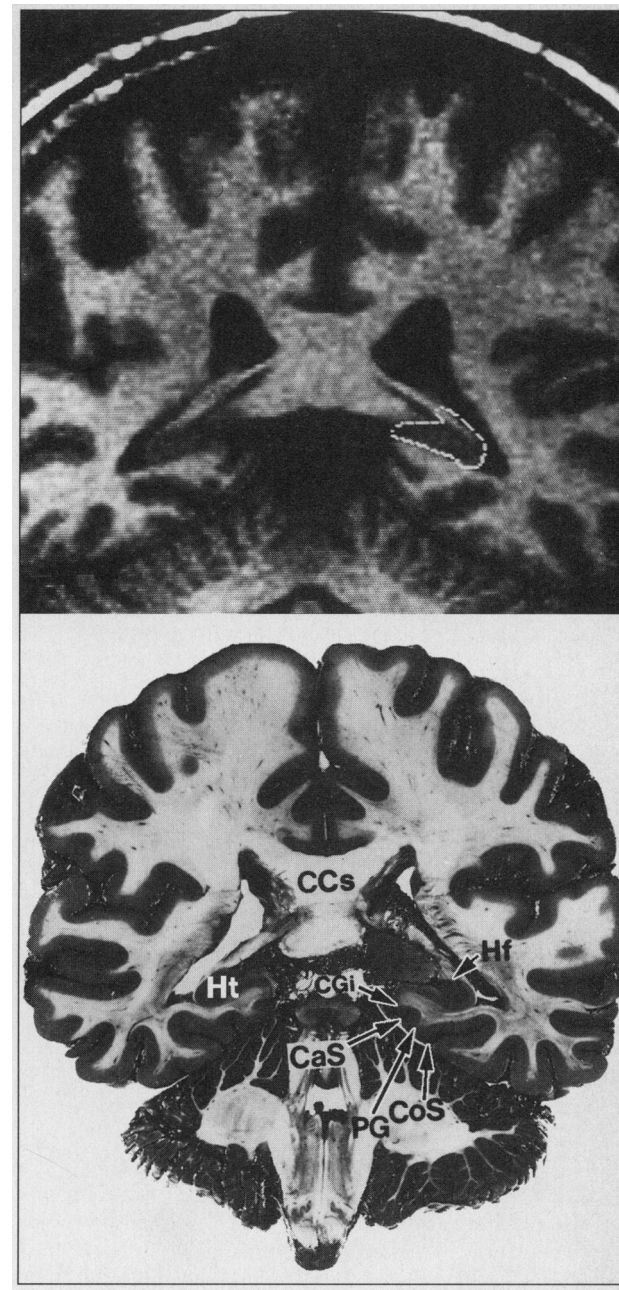

Figure 6. *Angled coronal sections of the cerebral hemispheres passing through the splenium of the corpus callosum and isthmus of the cingulate gyrus (adapted from Watson et al[20]). Top, Magnetic resonance image with the hippocampal tail outlined on the left. Bottom, Brain section showing the transition from fimbria of hippocampus to crus of fornix. CaS indicates calcarine sulcus; CCs, corpus callosum, splenium; CGi, isthmus of cingulate gyrus; CoS, collateral sulcus; Hf, fimbria of hippocampus; Ht, hippocampus, tail; and PG, parahippocampal gyrus.*

and preoperative memory function by means of a variety of neuropsychological test instruments.[11,46-52] In general, a significant relationship between left hippocampal volume and preoperative verbal memory function has been found in a number of studies.[11,48,49,52] Several studies have shown a correlation between hippocampal atrophy, as demonstrated on volumetric MR imaging, and poor memory function on the intracarotid amobarbital test.[47,50,51] Some studies have also shown a relationship between impaired nonverbal memory function and reduced right hippocampal volumes.[46,49]

While outcome after a temporal lobectomy is most often thought of in terms of postoperative seizure control, the most common serious cognitive complication of surgery is a postoperative decline in verbally mediated declarative memory after a dominant temporal lobectomy. The clear link between functional and anatomical integrity has led to the evaluation of hippocampal volumetric measurements as a means of predicting *postoperative* memory decline.[48,52-54] These initial studies showed that the neuroanatomical status of the hippocampus (ie, its volume), the patient's sex, and the hemisphere operated on independently influence the risk of a postoperative memory decline. Patients at greatest risk for a decline in verbal memory after a dominant left tem-

poral lobectomy are those with bilaterally symmetric severe atrophy of both the right and left hippocampi. The group at next greatest risk are patients with volumetrically normal hippocampi bilaterally (ie, no atrophy), and in this group the risk of a postoperative verbal memory deficit is greater in men than in women. The group at least risk for a postoperative verbal memory deficit after a dominant left temporal lobectomy is those with marked unilateral left hippocampal atrophy. However, in this group the risk is slightly greater for men than for women. These initial studies[48,52-54] correlating postoperative memory outcome with hippocampal volumetric measurements indicate that this technique may provide clinically useful prognostic information. Further studies will be necessary to confirm these findings and to determine whether the prognostic information provided by hippocampal volumetric measurements is complementary to that provided by the intracarotid amobarbital memory test.

CORRELATION WITH OUTCOME AFTER TEMPORAL LOBECTOMY

A significant relationship between MR imaging–based hippocampal volumes and seizure control after temporal lobectomy has been demonstrated.[55-58] It was well known in the pre–MR imaging era that a temporal lobectomy specimen that contained HS conferred a much higher probability of excellent postoperative seizure control for that patient than if the specimen was free of abnormality. However, that information was available only after the surgery had been performed. In the initial study on this topic,[55] 97% of patients in whom EEG lateralization was concordant with volumetrically determined unilateral hippocampal atrophy had a favorable surgical outcome (seizure free or nearly seizure free). The percentage of patients with a favorable outcome was only 42% in patients in whom the hippocampal volume measurements were nonlateralizing.

The most common radiological manifestation of HS seen in clinical practice is a *unilateral* atrophic hippocampus with a normal contralateral hippocampus. The surgical approach to temporal lobe epilepsy (temporal lobectomy) is also driven by the concept that HS is a *unilateral* phenomenon. However, autopsy studies and, more recently, quantitative MR studies indicate that HS is present *bilaterally* in a substantial percentage of patients with temporal lobe epilepsy.[1,59] For the sake of illustration, the entire spectrum of HS can be divided into 4 possible conceptual categories[59]: (1) unilateral hippocampal atrophy: HS is present unilaterally and the contralateral hippocampus is completely normal; (2) bilaterally asymmetrical hippocampal atrophy: HS is present bilaterally, but more severely represented on 1 side; (3) bilaterally symmetrical atrophy: HS is present and of equal magnitude in both hippocampi; and (4) volumetrically symmetrical normal hippocampal: neither hippocampus has changes of HS. This fourth category is conceptually useful in the context of this discussion because distinguishing mild HS from a normal hippocampus is not straightforward by visual inspection of MR images or by qualitative pathological analysis. These 4 groups represent conceptual points along a continuous distribution of hippocampal damage, ranging from severe HS to anatomically normal, in 1 or both hippocampi. Magnetic resonance imaging studies that have used absolute measures of hippocampal volume indicate that patients with unilateral HS (group 1 above) and patients with bilaterally asymmetrical HS (group 2 above) have a similar prognosis, which is excellent. In contrast, patients with bilaterally symmetrical hippocampal atrophy (group 3 above) and symmetrical normal hippocampi (group 4 above) have a significantly less favorable prognosis for a seizure-free outcome.[55,59] Nonetheless, a seizure-free outcome is possible in members of groups 3 and 4.

Arruda et al[58] recently studied 74 consecutive patients with temporal lobe epilepsy who were treated surgically and had preoperative volumetric MR imaging measurements of medial temporal structures. The patients were divided into 3 groups according to the volumetric MR imaging findings: unilateral atrophy (63.5% of the patients), bilateral atrophy (23%), or no atrophy (13.5%) of the amygdala, hippocampus, or both. Outcome was assessed at least 1 year after surgery, according to a modification of Engel's classification. Patients with unilateral medial temporal atrophy had significantly better results when compared with the other 2 groups ($P<.001$). Excellent results (class I or II outcome) were found in 93.6% of the patients with unilateral atrophy; in 61.7% of those with bilateral atrophy; and in 50% of the group with no significant atrophy of medial temporal structures. In addition, the ratio of hippocampal and amygdaloid volumes (ipsilateral-contralateral to the side of surgery) was significantly smaller in those patients who became seizure free or almost seizure free (class I or II) than in those with outcome classes III or IV. These data, in agreement with other studies,[55-57,59,60] indicate that the degree of asymmetry of medial structures, in those with unilateral and bilateral atrophy, may also be an important factor for postsurgical seizure control in patients with temporal lobe epilepsy. This suggests that a more atrophic hippocampus in the operated-on hemisphere, together with a healthier hippocampus on the unresected side, yields the best outcome, a finding that makes intuitive sense for cognitive function as well as for seizure control.[48,61]

In summary, MR imaging–based volumetric measurement of the amygdala and hippocampus not only aids in the determination of the side of seizure onset in nonlesional temporal lobe epilepsy but is also an important prognostic tool. For patients with unilateral atrophy, one can expect excellent results in 93% to 97% of the cases. Surgical outcome in those with bilateral atrophy is not as good but still represents a worthwhile option. Patients without significant atrophy or with bilateral symmetrical atrophy have the worst prognosis and thus remain a major challenge. The likelihood that some of the patients without atrophy have neocortical temporal lobe epilepsy helps to explain the poorer outcome in this group.

CLINICAL CORRELATIONS IN PATIENTS WITH EARLY CHILDHOOD INSULTS

Several studies have shown a significant relationship between hippocampal and amygdaloid atrophy, as deter-

mined with volumetric MR imaging, and a history of febrile convulsions in early childhood.[33,62,63] The interpretation of this observation remains controversial. One possibility is that the early febrile convulsion damages the hippocampus and is therefore a cause of HS. However, another possibility is that the child has a prolonged febrile convulsion because the hippocampus was previously damaged by a prenatal or perinatal insult.

A related question concerns whether HS is the cause of repeated seizures or is a consequence of them. Several investigations have shown that no significant relationship exists between atrophy of medial temporal lobe structures and the duration and frequency of seizures.[34,62-64] These studies, along with the febrile convulsion studies mentioned above, suggest that HS is caused by an insult early in life that remains relatively stable and that each subsequent seizure does not cause additional neuronal cell loss or progressive worsening of hippocampal atrophy.

A recent experimental study, in which Liu et al[65] performed a quantitative evaluation of neuronal density in the hippocampus in rats with long-term pilocarpine-induced seizures, provides support for these clinical studies with the use of volumetric MR imaging measurements. They found that the neuronal loss was dose dependent and primarily resulted from the acute pilocarpine-induced seizures. Chronic seizures did not produce any measurable additional loss in the regions examined in their study.

SPECIFICITY OF VOLUMETRIC MR IMAGING IN DETECTING HS

Several studies have investigated groups of patients with seizures originating in extratemporal and extrahippocampal sites with volumetric MR imaging used as a means of determining whether seizures emanating from sites other than the hippocampus and amygdala cause cell loss and subsequent atrophy of those structures, thereby leading to significantly reduced hippocampal and amygdaloid volumes.[19,22,66-70] In patients with long-standing epilepsy caused by extratemporal structural lesions, some studies showed no reduction in hippocampal volumes[22,66] and others found a low incidence (6%) of "dual pathology," a condition in which the patient has both a potentially epileptogenic structural lesion and HS.[67] Gilmore et al[19] also found volumetric MR imaging useful in differentiating patients with temporal lobe epilepsy from those with extratemporal epilepsy. In a recent multicenter study involving 167 patients with extratemporal or extrahippocampal temporal lesions, Cendes et al[68] found only 25 patients (15%) with dual pathology.

The studies mentioned above suggest an incidence of dual pathology in the range of 10% to 15% of cases of lesional epilepsy. However, certain types of structural lesions, such as developmental abnormalities, may exhibit a higher incidence of coexisting HS, in the range of 25% to 30%.[68] In a recent study by Watson et al,[13] 28% of their patients with pathologically proved HS exhibited dual pathology, and 80% (4/5) of those patients had neuronal migration disorders. This may account for some of the differences found in other studies.[71-73] The best approach to the treatment of patients with dual pathology is presently unknown, although it seems prudent to include both the sclerotic hippocampus and the structural lesion in the surgical resection if at all possible.[74] Studies involving large numbers of patients are needed to define the best surgical approach in this group of patients.

No reduction of hippocampal or amygdaloid volumes was demonstrated in studies by Watson and Williamson involving patients with long-standing primary generalized epilepsy[69] and secondary generalized epilepsy.[70] Therefore, significant reduction in hippocampal volumes appears to be a specific marker for HS.[75]

POSTOPERATIVE VOLUMETRIC MR IMAGING ANALYSIS

A few preliminary studies have examined the utility of postoperative volumetric MR imaging analysis in patients who have undergone temporal lobectomy.[60,76-78] The findings are certainly preliminary, but postoperative volumetric MR imaging studies are useful in the delineation of the extent of amygdaloid and hippocampal resection. It is hoped that this type of information may be useful in the future to help guide decisions concerning epilepsy surgery.

MR IMAGING OF THE HIPPOCAMPUS: QUALITATIVE VS QUANTITATIVE ASSESSMENT

A majority of cases of HS encountered for presurgical evaluation will have a clear-cut unilateral atrophic hippocampus with increased signal and a normal-appearing contralateral hippocampus. Several studies have shown volumetric MR imaging analysis of the hippocampus and amygdala to be very sensitive and specific in the identification of HS in this setting. However, simple qualitative visual analysis is also sensitive in this task, especially if the MR images are carefully and properly acquired.[2-6,79] In fact, a recent evaluation of fluid attenuated inversion recovery imaging sequences demonstrated an accuracy of 97% with pathological determination of HS as the criterion standard.[80] Measurements of hippocampal volume are *unnecessary* in this situation for *clinical* purposes. However, only a few studies have been completed that directly compare quantitative volumetric MR imaging of the hippocampus with qualitative visual assessment of the same MR images for the signs of HS. In the original work by Jack et al,[3] they found volumetric MR imaging to be slightly more sensitive than qualitative image analysis (76% vs 71%, respectively). However, more recent investigations using more high-resolution MR techniques have found volumetric MR imaging measurements to be significantly more sensitive than visual inspection alone.[81,82] Cendes et al[82] found that volumetric MR imaging showed a sensitivity of 92% compared with 56% for qualitative visual inspection. Similarly, Reutens et al[81] showed volumetric MR imaging to be at least 20% more sensitive than qualitative visual analysis. Therefore, volumetric MR imaging appears to offer a significant improvement in the detection rate of HS, although it is much more time consuming and must be done correctly to be accurate and reliable.

The greatest utility for volumetric MR imaging may be in the field of clinical research.[16] Magnetic resonance

imaging–based volumetric studies generate numerical data that permit better comparisons of the degree of atrophy of medial temporal structures in various subgroups of patients. The findings can be statistically correlated with various clinical measures and thereby lead to better discrimination and understanding of the underlying condition.

Furthermore, visual discrimination of a normal from an abnormal hippocampus is straightforward when one is clearly normal and the other is grossly abnormal, but the visual binary paradigm breaks down in the presence of symmetrical bilateral disease, mild unilateral disease, or both.[83] To accurately determine the presence and severity of hippocampal atrophy (HS) in both hippocampi, absolute quantitative measurements are therefore necessary. In addition, the preliminary results available indicate that the presence and severity of HS in both hippocampi may provide useful prognostic information about both postoperative seizure control and memory outcome.[48,52-59] At this point, the precise prognostic significance of bilateral or mild disease has not been fully elucidated. A compelling area for research at this time therefore is to determine the precise relationship between outcome and the *degree* of damage in *both* hippocampi. Magnetic resonance imaging–based hippocampal volume measurement is an ideal technique for the investigation of these important clinical issues.

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