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Guidance for Sponsors
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Temporal Lobe Epilepsy and Volumetric MRI in Clinical Trials

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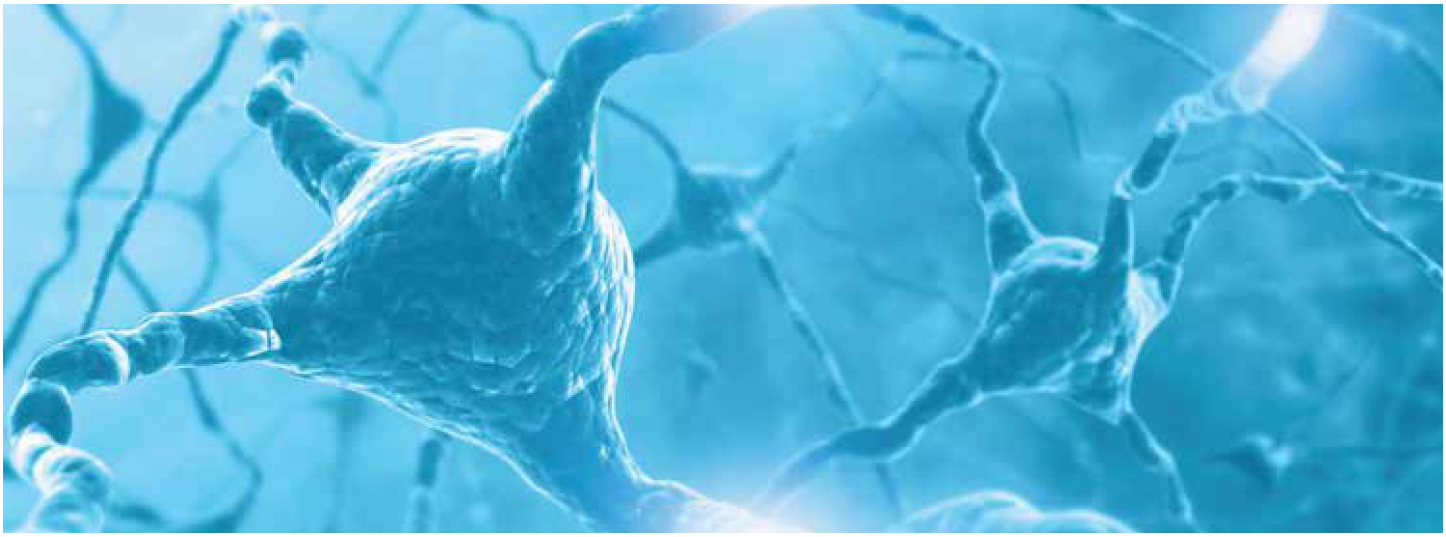

Temporal lobe epilepsy caused by hippocampal sclerosis is one of the most common forms of drug-resistant focal epilepsy, and one of the most treatable when it is correctly identified. Visual reading of MRI can miss mild or bilateral hippocampal atrophy, which makes patient selection the weak link in many trials. Quantitative volumetry with FDA-cleared software, acquired on a harmonized epilepsy protocol, converts a subjective impression into a numerical biomarker. It can set inclusion thresholds, stratify severity, predict surgical outcome and, potentially, measure the effect of new drugs, ablation and neurostimulation devices.

Temporal Lobe Epilepsy

Hippocampal sclerosis is the most common pathology in drug-resistant temporal lobe epilepsy, and it is typically refractory to medication. The International League Against Epilepsy (ILAE) classifies it into types according to the pattern of neuronal loss and gliosis.[1] On structural MRI, hippocampal sclerosis is recognized by atrophy, increased T2 signal reflecting gliosis, and loss of internal architecture. Selecting patients who may benefit from resection, laser ablation or an implanted stimulator begins with an accurate diagnosis.

A diagnosis is established when scalp electroencephalography (EEG) and structural MRI agree. Candidates then undergo neuropsychological testing and language and memory lateralization to avoid resecting eloquent tissue. When EEG and MRI are concordant, 60 to 80% of patients become seizure-free after temporal lobe resection; when they are discordant, the rate falls below 60%, and invasive EEG, magnetoencephalography or PET may be required.

Diagnostic Challenges in Patient Selection

Image quality comes first. The ILAE's 2019 HARNESS-MRI protocol recommends three core acquisitions: isotropic 3D T1-weighted and 3D FLAIR sequences at about 1 mm, and a high-resolution coronal T2-weighted sequence perpendicular to the long axis of the hippocampus.[2] These sequences are available on most scanners and suit multicenter trials.

Even on excellent images, visual assessment has limits. An experienced neuroradiologist can generally detect hippocampal volume loss of about 15%, relying on an internal threshold built from years of reading. Mild bilateral atrophy is especially difficult, because readers instinctively judge size by asymmetry. Gliosis and loss of internal architecture are helpful findings, but they are less specific than atrophy.

Volumetric MRI as a Quantitative Biomarker

Automated volumetry compares each hippocampus with an age-matched normative database and calculates an asymmetry index between the two sides. In a study of patients with temporal lobe epilepsy, fully automated volumetry performed com-

parably to manual measurement and enhanced visual analysis in both community and tertiary care settings.[3] The ILAE notes that volumetry corrected for head size and normalized against healthy controls is more sensitive than visual reading.[2] Several such tools are FDA-cleared, including NeuroQuant, most recently under 510(k) K241098.[4]

Because each hippocampus is compared with normative data, volumetry can establish bilateral disease and grade the severity of each side, where the asymmetry index alone is not useful. In a trial, the measurement can set a numerical inclusion threshold or place qualified subjects in prespecified severity strata.

Patient Categorization in Trials

In patients with discordant EEG and structural MRI, quantitative volumetry identifies candidates more accurately and stratifies disease objectively. Patients with normal volumetric and structural MRI present a different problem. Some have hippocampal sclerosis supported by EEG, magnetoencephalography or PET; others may not. The situation resembles "scans without evidence of dopaminergic deficit" in Parkinsonism, where many patients were later found to have other conditions. If MRI-negative patients are enrolled, they should be characterized as such so that they do not dilute the trial's results.

Volumetry and Therapeutic Response

Volumetry also carries prognostic information. The magnitude of hippocampal asymmetry has been correlated with memory outcome after resection: patients with greater asymmetry, especially left-sided atrophy, were less likely to experience memory decline.

Minimally invasive treatment is expanding. A meta-analysis of ablative therapies for mesial temporal lobe epilepsy reported seizure freedom in 55% of patients treated with MRI-guided laser interstitial thermal therapy, with major complications in 2.3%.[5] Responsive neurostimulation, approved by FDA through premarket approval P100026, detects seizure onset and delivers targeted stimulation to as many as two foci.[6] Whether volumetric change tracks therapeutic response after ablation, neurostimulation or new drugs is a question well suited to controlled trials. Artificial intelligence is extending detection further: the MELD Graph model has improved detection of subtle focal cortical dysplasia, another common cause of drug-resistant epilepsy.[7]

Guidance for Sponsors

Imaging an epilepsy trial

- **Harmonize acquisition.** Specify the HARNESS-MRI sequences at every site.[2]
- **Quantify, do not estimate.** Use FDA-cleared volumetry against age-matched norms.[3,4]
- **Prespecify thresholds.** Define volumetric inclusion criteria and severity strata in the protocol.
- **Characterize MRI-negative patients.** Analyze them as a separate stratum.
- **Read centrally.** Combine neuroradiologist review with quantitative output.[8]

Summary

Quantitative hippocampal volumetry turns a subjective impression into an objective biomarker. It improves the selection and stratification of patients with temporal lobe epilepsy, predicts outcome after surgery and may measure response to ablation, neurostimulation and new drugs. For sponsors, a harmonized protocol and central quantitative analysis are now the foundation of a credible epilepsy trial.

About the Author

Dr. Barry Menick, a board-certified neuroradiologist, wrote the original edition of this issue at Intrinsic Imaging. He earned his undergraduate and medical degrees at Duke University and completed his residency in diagnostic radiology and a two-year neuroradiology fellowship at the Hospital of the University of Pennsylvania. A Senior Member of the American Society of Neuroradiology since 1991 and a member of the American Society of Functional Neuroradiology, he has a particular interest in quantitative imaging of neurodegenerative disease and functional imaging of brain tumors.

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About Intrinsic Imaging, LLC

Intrinsic Imaging is an ISO certified medical imaging CRO and imaging core lab providing comprehensive services in support of Phase I-IV clinical trials and Class I, II, III medical device trials. Intrinsic Imaging is also a world leader in conducting Artificial Intelligence studies. With its team of more than 650 board-certified and fellowship-trained physicians, Intrinsic Imaging's team has sub-specialization in all therapeutic areas, including Cardiovascular, Central Nervous System,Gastroenterology, Musculoskeletal, Oncology and Ophthalmology. Certified by the British Standards Institution (BSI), Intrinsic Imaging is the only company in the world to hold five ISO certifications specifically for providing imaging core lab services on clinical trials. For more information, please visit www.IntrinsicImaging.com.

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