Epilepsy is the fourth most common neurological disorder in all ages. According to the Epilepsy Foundation, 1% of the population is expected to develop epilepsy before 20 years of age. Extra-temporal cortical resection is the most common curative epilepsy surgery in infants* and children, whereas temporal lobectomy is the most common in adults. Children with intractable epilepsy may benefit from early surgical intervention to avoid the potential negative effects of continued seizures and prolonged use of anti-epilepsy drugs on cognitive and psychosocial development and to increase the chances of post-operative neurological reorganization due to the inherent functional plasticity of the pediatric brain. Tellez-Zenteno et al. surveyed 3557 (697 non-lesional, 2860 lesional) temporal and extra-temporal epilepsy data from children for whom structural MRI was used to define the patient as being lesional or non-lesional and who then underwent surgery [1]. The meta-analysis revealed the seizure free post-surgery rate was 45% for non-lesional patients and 81% for lesional patients. This highlights the importance of successfully locating, and characterizing, the epileptogenic zone (EZ), which is defined as the volume of brain tissue responsible for the generation of seizures and whose removal consequently leads to freedom from seizures. It is important to characterize the structural lesion because the spatial relationship of the lesion to the EZ varies between different types of lesions. For most brain

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1A Inversion recovery and T2-weighted images acquired with high spatial resolution on a 3T MAGNETOM Trio scanner. A subtle lesion (red arrows) can be seen that is hypo- and hyper-intense on the IR and T2-weighted images respectively.
tumors, removal of the lesion, including the immediate margins of tissue around the lesion, will lead to freedom from seizures in a high percentage of patients. However, in the case of focal cortical dysplasia, removal of the lesion and its margins frequently does not lead to freedom from seizures, implying that the EZ extends beyond the visible lesion in this case. As with any surgery there are potential risks as well as benefits, in particular that the epileptogenic focus may share, or be in close proximity, to eloquent cortex. Thus it is not uncommon for patients to suffer from varying degrees of neurocognitive decline post-surgery. For patients with temporal lobe epilepsy (TLE) the decline is predominately manifested as verbal or visual memory impairment [2–5]. For example, one study showed that TLE patients suffered an average of 11% verbal memory decline following TL resection [4]. Another, more recent, study revealed that although group level comparison shows no significant verbal intellectual loss, roughly 10% of TLE children experienced a significant decline in verbal functioning following TL resection [5]. Hence thorough and meticulous presurgical assessments are necessary to address both aspects of the surgical outcome, i.e., post-surgical seizure activity and neurological functioning. Neuroimaging is now routinely prescribed for TLE patients who are potential candidates for temporal lobectomy. The neuroimaging assessment includes video EEG monitoring, structural neuroimaging (MRI), functional cerebral imaging such as fMRI, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). The results of these evaluations can be used individually, or collectively, to:

1) Localize and characterize the epileptogenic focus and thus help the physician to determine if surgical resection of the extratemporal cortex is appropriate.

2) Identify both the laterality of functions such as language and the location of patient-specific, functionally important, cortical regions and white matter tracts that should, if possible, be spared by surgery.

**Localization of epileptogenic focus**

The brain lesions associated with pharmacoresistant epilepsy are often subtle and require special expertise for their detection and characterization. In addition, the use of a dedicated epilepsy protocol, rather than a standard brain protocol, has been shown to offer improved lesion detection [6]. Dedicated TL epilepsy protocols include high spatial resolution thin slice, T1 and T2-weighted coronal and axial imaging with the coronal images being acquired in an oblique plane perpendicular to the long axis of the hippocampus when evaluating TLE. It has also been shown that the use of a 3T magnet and phased array coils further improves the sensitivity of lesion detection, when compared to 1.5T results [7]. Figure 1 illustrates two cases where epileptogenic foci were identified on high resolution anatomical MR images. To date, most studies have shown that interictal diffusion imaging is not helpful for lesion localization [8]. Changes in the diffusion tensor have been detected.
but in general do not reach statistical significance even at the group level [9]. This may be, in part, due to partial volume effects from the poor spatial resolution typically used for diffusion studies. The development of higher resolution techniques for diffusion imaging may change this in the future.

In a small portion of our epilepsy surgery population, PET is used to assist the localization of epileptogenic focus. Due to the poor resolution of PET images, CT and/or MRI are also performed on this group of patients. The PET images are then coregistered with CT and MR results in order to allow the anatomical location of areas of poor perfusion to be more accurately identified. Figure 2 shows a case where an epileptogenic lesion was identified on the fused PET-CT and PET-MR images.

Another technique that is used more frequently at our institution for the localization of the EZ is SISCOM (Subtraction Ictal SPECT Co-registered to MRI). This technique combines SPECT studies of a tracer that reflects cerebral perfusion, with the studies being acquired both ictally (during a seizure) and an interictally (between seizures) [10, 11]. Conventionally, side-by-side visual analysis of ictal and interictal SPECT images can be used for lesion identification. However, the interpretation of the images can be quite difficult due to differences in the injected dose, tracer uptake and decay, patient head position, and slice positioning. To address these problems, the SISCOM technique registers the two SPECT scans using a mutual information based registration algorithm (we do an initial crude manual registration in order to avoid problems with local maxima of the registration algorithm) and then normalizes the two SPECT scans prior to computing a difference image that represents a semi-quantitative map of the cerebral blood flow changes occurring during the seizure [10]. Unfortunately, the poor spatial resolution and contrast of the SPECT images complicate the determination of the exact anatomical location of any seizure focus detected on the differential image. For this reason, the differential image is subsequently coregistered to and then represented as a color overlay on a T1-weighted volumetric MR image in order to better localize the lesion. One study showed that the localization of epileptic foci is 88.2% for SISCOM but only 39.2% for side-by-side inspection of SPECT images [11]. Figure 3 shows the SPECT data, the processed difference image and the fused SISCOM images for a patient with TLE. Using the information from SISCOM and/or video-EEG to further refine the epileptic protocol can allow an experienced radiologist to detect focal cortical dysplasia in patients who were considered non-lesional on the standard epilepsy protocol [12]. While SISCOM can be a very useful technique, it is rather time and labor intensive as the injection must be performed promptly after the seizure for the technique to work properly. The seizure must also be of sufficient duration and of the type that typically occurs in that patient (video EEG is required to verify this).

For patients scheduled for TL resection, intracranial EEG recordings are performed in some cases in order to provide additional information of the location of the epileptogenic focus, or to better define functional cortex that needs to be spared. If lesions have been identified by structural MRI or an area of abnormal perfusion has been identified on the SISCOM study, the results of these studies are used to guide the grid placement. In our hospital, we used the Stealth station navigation system by Medtronic to guide the electrode grid placement. For the structural images, the procedure is straightforward. For the SISCOM images, the procedure is a little more involved and requires the following steps:

1) Register the differential SPECT image to the anatomical MRI.
2) Color code the differential image.
3) Fuse the color coded SISCOM to the MR image on the navigation system.

After grid placement, the patients are observed using continuous EEG video monitoring in order to detect seizures. Once a seizure is identified, the electrodes showing the strongest activity at the time of the seizure can be localized. In order to identify the spatial location of these electrodes a CT scan of the electrode grid is obtained, preferably performed immediately post-surgery in order to minimize the swelling caused by post-surgical edema. Co-registering of the CT scan to a structural MRI volume is performed using the fusion tool on the MultiModality Workplace (Leonardo). The neurologists and radiologists can then determine the spatial location of the electrodes closest to the source of the seizure activity. Figure 4 illustrates a case of CT grid and MRI co-registration.
Identification of laterality and functional cortex

Traditionally, a neuropsychological evaluation called the Wada test is performed to determine which side of the brain is responsible for certain vital cognitive functions, specifically language and memory. The Wada test consists of a standard neuropsychological assessment performed in conjunction with intracarotid injections of sodium amytal. The drug is injected into one hemisphere at a time inactivating language and/or memory function in that hemisphere in order to evaluate the contralateral hemisphere. The patient is engaged in a series of language and memory related tests during and after the Amytal effect. The results of the test are then used to estimate the potential functional effects of the surgery in language and memory, and help in planning the surgical approach. When localization of function to a particular area of the brain is required electro-cortical stimulation (ECS) was traditionally used. This test requires that electrodes are placed on the surface of the brain and direct stimulation of the electrodes on the exposed brain is then performed to map regionally specific function. As the patient has to interact with the surgeon for this test the actual mapping has to be performed under local, rather than general, anaesthetic.

Recently, fMRI has emerged as a non-invasive alternative method for lateralizing the language and motor networks, and to a lesser degree – memory, in cooperative children with epilepsy [13–15]. Brain mapping with fMRI has also revolutionized the evaluation of patients undergoing epilepsy surgery by providing a non-invasive method for identifying critical brain areas to spare during resection and offering a powerful tool for studying neural plasticity. There are numerous advantages of fMRI over other conventional modes in terms of language mapping: fMRI is non-invasive, does not carry the risk of either the WADA test or ECS, and different paradigms can be utilized to map different cognitive functions. Unlike the WADA test and ECS, fMRI can be readily repeated to confirm findings, and can both lateralize and localize different aspects of language functions. Correlation of fMRI results with those obtained using ECS show good, but not perfect, agreement. For language paradigms, when allowing for up to 10 mm between the activated areas using the two techniques, the sensitivity of fMRI to detect the language areas was between 67 and 100% depending on the paradigm [16]. It should be noted that the intrinsic resolution of fMRI studies is typically in excess of 3 mm and the smoothing used in the post-processing increases this to 5 mm or more.

For the pediatric population, impaired language is the most common adverse consequence of TL surgery. At our institution, language mapping is performed using one or more of three novel fMRI paradigms. The language paradigms were developed in conjunction with the Children’s National Medical Center and are designed to target both expressive and receptive language processing. They were specifically developed for the assessment of the BOLD response in the language cortex of children and young adults under clinical conditions. Specifically, the following three tasks are employed, each using a block design:
This case illustrates CT grid and MRI co-registration. Registration and initial visualization were achieved with 3D task card on a Siemens MultiModality Workplace (Leonardo). The electrodes can be seen as yellow/white area on the fused image due to their high intensity (i.e. high attenuation) on the CT images, areas of bone can be seen in red due to the relatively high attenuation of bone. The 3D representation was generated using in-house software which segments the CT scan to remove the bone and brain tissue and then provides an overview of the position of the grids on the surface of the brain.
a) Auditory category decision task (AU\textsubscript{CAT}): A category is presented followed by a series of words. Participants are instructed to press a button if a word belongs to the specified category;  
b) Auditory description decision task (ADDT): A description of an object is presented to the participants. The participants are required to press a button when the description is consistent with the matched object;  
c) Listening to stories (Listening): Stories based on Gray Oral Reading Test are presented with pseudorandom inserted beeping sounds. Participants are instructed to press a button when a beep is heard while listening to the story. The participants are told that they will be questioned on the story after the scan in order to try and ensure that the participant pays attention to the story.  

The rest condition for all three paradigms consists of reverse speech of the experimental condition with intermittent beeps as cues for button presses. All paradigms comprise five 30 second task blocks and five 30 second control (rest) blocks, resulting in a total duration of five minutes. Participants are instructed to press a single button for correct answers or upon hearing a beep (70\% true and 30\% false for task condition, matching number of button pushes for the corresponding control condition) during the course of the experiment. The responses are collected and inspected for the purposes of task monitoring and evaluation of response accuracy. The paradigms are also graded for skill and the appropriate version is selected for each participant based on his/her neuropsychological test score. All MRI scans are conducted on a Siemens 3T MAGNETOM Trio scanner equipped with 8-channel receive only head coil. A gradient echo EPI with TR = 3 sec and TE = 36 milliseconds and a nominal spatial resolution of 3.0 mm\textsuperscript{3} is used for the fMRI studies. Oblique axial slicing is chosen for the fMRI acquisitions in order to increase coverage and reduce susceptibility effects. Inline fMRI analysis is done within the BOLD task card. Pediatric neuroradiologists and neuropsychologists use these results to determine the laterality of language and to locate the cortical regions implicated in language. The results are communicated to the neurosurgeons so that an optimized surgery plan can be developed. In some cases, the fMRI results along with CT grid and/or SISCOM results are all uploaded to the navigation system and used for realtime surgery guidance. For such purposes, the fMRI data is processed with FSL (www.fmrib.ox.ac.uk/fsl) and the statistical parametric maps are exported in DICOM format, which is required by our navigation system. Briefly, the fMRI data is pre-processed using the standard options and then analyzed using a general linear model, the resulting spatial statistical maps are then projected back to the corresponding anatomical MRIs and fed to the navigation software. Figure 5 shows a case where we simultaneously overlaid a CT grid scan (segmented to exclude brain tissue and bones) and the ADDT fMRI result on the anatomical MRI image. Diffusion tensor imaging (DTI) can also be used to map the major white matter pathways which project into the temporal lobe and this information can be used by the surgeons to try and spare these regions and hence preserve the communication with other regions of the brain. To achieve this goal,
white matter tracts connecting vital cortical regions (as identified by fMRI) are traced on DTI images, and those tracts are then uploaded onto the navigation system for surgical guidance. The DTI data is acquired axially using a 30 directions EPI sequence (b = 1000 sec/mm²), 5 b = 0 scans, TR/TE = 8900/96 ms, a parallel imaging factor of 2 and a nominal spatial resolution of 2 mm³.

Our radiologists first review the DTI results produced by Neuro3D on the Siemens console and determine if DTI guidance is appropriate. If so whole brain tractography using the FACT algorithm is performed. The relevant fiber tracts are generated using the fMRI results as seed/target points. Binary masks are then created from the fiber tracts (voxels in the path of the tracts are assigned value 1 while others are assigned value 0). The resulting binary images are exported as DICOM images and sent to the navigation system (in a similar manner to the SISCOM and fMRI results) where they can be used to highlight the fiber tracts to be avoided during surgery.

These imaging techniques are now a routine part of the clinical workup for all of the epilepsy patients at our institution. They have greatly improved our ability to detect focal lesions, to minimize the detrimental effects of epilepsy surgery and to provide improved guidance to the neurosurgeon.

References

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*MR scanning has not been established as safe for imaging fetuses and infants under two years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.