Imaging Epilepsy

Andre Lagrange MD PhD ABCN FANA
Advanced MRI
Epilepsy Protocol

- Volumetric T₁
- Thin cut, no skip Inversion Recovery T₁ (aka SPGR)
- Thin cut FSE- T₂ or FLAIR perpendicular to hippocampus

- Highly sensitive: >95% detection histopathologically defined MTS (Kuzniecky Neurology 1997)
- Can have false positives, especially if bilateral (Labate Neurology 2013)

- Axial FLAIR
- Sagittal T₁
- Contrast may not be needed
Is stronger always better?

- 3T and higher allow for faster scans,
- Greater signal:noise
- May be more sensitive to magnetic field inhomogenities
  - Can give false positively abnormal changes in signal intensity
MRI & VNS

- Potential Problems
  - Heating
  - Device reset that could theoretically clear historical data (serial number, implant data, stimulus parameters)
  - Magnet mode activation during scan - prevented by setting current to 0 mA
  - Distorted images
    - Product insert specifically says to avoid use of an open MRI or trying to image the area actually containing the VNS device (usually C7-T8).

- Managements
  - Coordinate the scan with radiology (you might need to get their approval before ordering the scan
  - Interrogate the device prior to scan, write down the settings
  - Re-interrogate and possibly reprogram after the scan
Incidental MRI findings

<table>
<thead>
<tr>
<th>Neoplasia (n=19 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>72</td>
<td>345</td>
<td>0.29 (0.13 to 0.51)</td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>27</td>
<td>667</td>
<td>0.15 (0.09 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>8</td>
<td>2000</td>
<td>0.05 (0.02 to 0.09)</td>
<td></td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>5</td>
<td>3333</td>
<td>0.03 (0.01 to 0.06)</td>
<td></td>
</tr>
<tr>
<td>Lipoma</td>
<td>6</td>
<td>2500</td>
<td>0.04 (0.02 to 0.07)</td>
<td></td>
</tr>
<tr>
<td>Epidermoid</td>
<td>3</td>
<td>3333</td>
<td>0.03 (0.01 to 0.06)</td>
<td></td>
</tr>
<tr>
<td>Unspecified neoplasm</td>
<td>14</td>
<td>1111</td>
<td>0.09 (0.03 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>Any neoplastic incidental finding (n=19 559)</td>
<td>135</td>
<td>143</td>
<td>0.70 (0.47 to 0.98)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structural vascular abnormalities (n=15 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm</td>
<td>67</td>
<td>286</td>
<td>0.35 (0.13 to 0.67)</td>
<td></td>
</tr>
<tr>
<td>Cavernous malformation</td>
<td>23</td>
<td>625</td>
<td>0.16 (0.10 to 0.23)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>7</td>
<td>2000</td>
<td>0.05 (0.01 to 0.10)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory lesions (n=15 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite demyelination</td>
<td>9</td>
<td>1667</td>
<td>0.06 (0.02 to 0.15)</td>
<td></td>
</tr>
<tr>
<td>Possible demyelination</td>
<td>4</td>
<td>3333</td>
<td>0.03 (0.00 to 0.07)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cysts (n=15 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachnoid cyst</td>
<td>99</td>
<td>200</td>
<td>0.50 (0.21 to 0.87)</td>
<td></td>
</tr>
<tr>
<td>Colloid cyst</td>
<td>2</td>
<td>2500</td>
<td>0.04 (0.01 to 0.07)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other abnormalities (n=15 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiari I malformation</td>
<td>71</td>
<td>417</td>
<td>0.24 (0.04 to 0.58)</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>15</td>
<td>1000</td>
<td>0.10 (0.03 to 0.19)</td>
<td></td>
</tr>
<tr>
<td>Extra-axial collection</td>
<td>4</td>
<td>2500</td>
<td>0.04 (0.01 to 0.07)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any non-neoplastic incidental finding* (n=15 559)</th>
<th>Number with abnormality</th>
<th>Number needed to scan</th>
<th>Prevalence (%) (95% CI)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>meta-analysis of 20,000 controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Neoplasm
  - Meningioma 0.3%
  - Pituitary adenoma 0.15%
  - Other 0.2%
- Vascular
  - Cavernoma 0.16%
  - AVM 0.05%
  - Aneurysm 0.35%
- Arachnoid Cyst 0.5%
- Chiari I 0.24%
- Hydrocephalus 0.1%

Morris Z et al. BMJ 2009;339:bmj.b3016
Prevalence incidental MRI findings by age

Morris Z et al. BMJ 2009;339:bmj.b3016
MRI findings in adults seen at an epilepsy clinic

Potentially epileptogenic MRI in adults
- ≈ 50% had abnormal MRI,
- ≈ 25% had potentially epileptogenic lesion
  - Focal seizures 53%
  - Generalized Sz 13%
    - IGE -8%
    - PNES + syncope – 8%
- Lesion types
  - 50% were encephalomalacia
  - 15% tumors (mostly meningiomas)
  - 10% cavernomas
  - 8% MTS
  - 8% FCD or heterotopias

Hakami et al 2013.

(A) left frontal gliosis and encephalomalacia
(B) Right frontal periventricular heterotopia
(C) Right anterior cingulate gyrus cavernoma.
(D) An enhancing meningioma.
(E) AVM
(F) right hippocampal sclerosis.
Hippocampal anatomy
Mesial Temporal Sclerosis

1) Hippocampal atrophy
2) Increased T2 signal
3) Altered configuration
   1) Normal hippo is oval
   2) Abnormal can be flattened & tilted
4) Loss of internal structure-
5) Look at surrounding brain
   1) Enlarged lateral ventricle
   2) Atrophy of ipsalateral fornix & mammillary body (red arrows)
Hippocampal Imaging

Atrophy is more specific than T2 changes

- 99 young adult controls compared to 51 pt with TLE
  - FLAIR changes (uni or bilateral) 48% TLE vs 29% controls
  - Unilateral atrophy 40% TLE vs 1% in controls
Sometimes MTS is more apparent on axial views
Cortical Development

- Radial migration
  - Subcortical, funnel shape transmantle sign
  - polymicrogyri
Cortical Dysplasia Classification 2013

- **Type 1**
  - 1a: abnormal radial lamination of CTX → small hemisphere
    - Microscopically: Microcolumns are maintained, but border to white matter is blurred
    - Radiologically can appear as just a diffusely smaller hemisphere
  - 1b: abnormal tangential lamination of CTX
    - Failure to create normal 6-layered cortex.
  - 1c both radial & tangential lamination

- **Type 2**
  - 2a dysmorphic neurons
  - 2b dysmorphic neurons + balloon cells

- **Type 3 (FCD-plus)**
  - 3a FCD + MTS
  - 3b FCD + adjacent tumors
  - 3c FCD + adjacent vascular malformation
  - 3d FCD + adjacent other malformation
Focal cortical dysplasia (FCD) an obvious example

Figure 1 | High-resolution 3T axial sections showing FCD Palmini type IIb in the

- Note the combination of abnormal cortical configuration, thickness and signal
- Higher grade FCDs tend to much easier to appreciate on MRI

Bernasconi 2011
FCDs
Sulcal abnormalities

- The majority (≈85%) of small FCDs found at the bottom of especially deep sulci
  - Blurred gray-white border
  - Transmantle sign

Strongly consider including depth electrodes for planning invasive recording, may be more likely than subdural grids to record directly from the lesion Bernasconi 2011
Subtle Transmantle sign with FCD 2a

Bernasconi 2011
Clear transmantle sign in FCD 2b

Blue arrow cortical thickening and loss of sharpness of the cortical-subcortical transition
Red arrow transmantle sign + T2 hyperintensity
FCD

3T Phased Array can help

Standard 1.5T head coil  3T phased array
Be sure to look at the proper sequences

Standard T1

SPGR (aka spoiled gradient echo or FFE)
What's this?
Cavernoma (1)
### Dating blood on MRI

**Dr Dre’s Musical Mnemonic**

♪ Id-Dy, Bi-Ddy, Ba-By, Da-Ddy ♫

<table>
<thead>
<tr>
<th>Age of blood</th>
<th>T1 signal</th>
<th>T2 signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute (min)</td>
<td>Isointense</td>
<td>Dark</td>
</tr>
<tr>
<td>Acute (hours)</td>
<td>Bright</td>
<td>Dark</td>
</tr>
<tr>
<td>Subacute (days-wks)</td>
<td>Bright</td>
<td>Bright</td>
</tr>
<tr>
<td>Chronic (wks-mos)</td>
<td>Dark</td>
<td>Dark</td>
</tr>
</tbody>
</table>
Low grade tumors in temporal lobe

- Gliomas
- Gangliogliomas
- Oligodendroglioma
- Dysembryoplastic neuroepithelial tumor
  - Dark on CT, may have calcifications
  - Variable contrast enhancement (about 30% enhance)
  - May be associated with FCD
Meningiomas

Extraxial, compressive
Look for the dural tail

Hakami et al 2013.
Gangliogliomas & DNETs
(hard to differentiate in imaging)

Both DNET & Gangliogliomas are commonly found in temporal lobe tumors associated with epilepsy in kids/young adults. Both have variable contrast-enhancement and cystic components. They tend to be T1 dark, T2 bright. A portion (≈25%) of DNETs also have calcification.
Oligodendrogliomas

- T1 dark, T2 bright
- May have foci of T1 bright signal due to intratumor bleeding
- Usually calcified, best seen on CT. May be shell-like, ringlike, or nodular.

Cendes CONTINUUM: 2013.
Calcifications may be seen on CT (A), but not necessarily on MRI (B). Susceptibility-weighted images can sometimes pick up calcium (not yet reliable).

Zulfiqar M et al. AJNR Am J Neuroradiol 2012;33:858-864
fMRI- assumes intact neurovascular coupling

- Functional MRI (fMRI) visualizes blood flow changes reflecting activation of brain regions.
  - Assumes neurovascular coupling is intact
- In a basic fMRI study, a subject alternates between an active task (for example naming animals) and an inactive (or control) state.
- Comparison of active and inactive images shows changes in blood flow reflecting activation.
fMRI- specific testing techniques

- Word Generation
  - from Categories
  - From Letters

- Reading
  - Descriptions of nouns
  - Reading pseudowords
  - Listen to a story
Magnetoencephalography (MEG)
Surface EEG Potentials

Intracellular Recording

Extracellular Recording

DENDRITE

SOMA

Axon from contralateral cortex
MEG properties

MEG is essentially looking at the same physiological phenomena as EEG, just in a different way...

- **EEG**
  - Reports radial electrical signal (top of sulci)
  - Sensitive to variable tissue conductivity
  - Relatively unaffected by distance

- **MEG**
  - Reports tangential electrical signal (within sulci)
  - Relatively unaffected by variable conductance (breach)
  - Very sensitive to distance
  - E.g. MEG only detects about 25% of mesiotemporal spikes seen on EEG
MEG application

- Variable sensitivity & specificity, and some of the information content overlaps that of EEG
  - 5-15% of patients- spikes on only MEG or EEG (both both)
  - Consider if suspected neocortical epilepsy & inconclusive EEG
    - Kaiboriboon 2010 showed MEG $\oplus$ in 60% with nonlocalizing EEG
- Most experts advocate using MEG to fine-tune surgical plan
  - Adjust grid placement
  - MEG source overlaps lesion on imaging $\Rightarrow$ ↑ prognosis
  - MEG shows multiple sources + nonlesional MRI ↓ prognosis
  - Multifocal MRI- MEG can help determine which are epileptogenic

Stefan, Rampp, Knowlton 2011
fMRI

- $\uparrow$ neural activity $\rightarrow$ $\uparrow$ local perfusion $\rightarrow$ $\uparrow^{\text{oxy/deoxy}}$ Hb

- Assumes neurovascular coupling is intact
  - May not be true in older individuals
  - Could theoretically be altered by trauma, tumor
  - The few studies that looked at this methodically in epilepsy, have found intact neurovascular coupling
fMRI (2)

- Compares BOLD signal during specific task (reading words) vs rest state (random sequence of symbols, [*$^)*@#!])
- Requires subject can lie still & perform the task (e.g. reading without glasses)

Name object based on written description
MRI modalities used primarily for research
Voxel based morphometry

- Compare to a normative dataset
  - After correction for inhomogenities, classifying voxels by tissue type then registered to a normative dataset
  - One approach is to take areas with > 2 SD signal intensity over normal data.
  - Keep in mind- about 60% of FCD pts have areas of abnormal signal outside of the epileptogenic region
    - False positives vs nonepileptogenic abnormalities
MRS

- Quantify neuronal integrity by measuring N-acetylaspartate vs choline/creatine
- Can only cover a few large voxels (rather than whole brain)
  - Poor signal: noise
  - Requires long acquisition times
- Use with caution (if at all)
  - Low resolution
  - Only a few areas sampled
  - Affected by neuronal density
  - Dynamic marker: you might get different results from the same patient
DTI
Ictal SPECT & SISCOM
Ictal SPECT- an easy case
SPECT

- SISCOM = subtracted Ictal SPECT Coregistered to MRI
- Required: ictal, interictal SPECTs and high res T1 MRI
- Best to use it to test/fine-tune a specific hypothesis usually in preparation for intracranial iEEG
  - E.g. seizures start in the right frontal area - yes/no
  - If yes, can we further limit the area of ele
Value of ictal SPECT

- 85% sensitivity & 75% specificity relative to intracranial ictal EEG

- In frontal or parietal epilepsy SISCOM can double the chances of finding seizure onset even if ictal scalp EEG is inconclusive (Lee 2006)

### TABLE 6
Comparative Sensitivity and Specificity of Neuroimaging Methods in Patient Group by Intracranial EEG Standard (n = 26)

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT (diff)</td>
<td>86</td>
<td>75</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>SPECT (ii, visual)</td>
<td>50</td>
<td>75</td>
<td>91</td>
<td>22</td>
</tr>
<tr>
<td>SPECT (i, visual)</td>
<td>73</td>
<td>75</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>MRI</td>
<td>60</td>
<td>75</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>PET (n = 20)</td>
<td>78</td>
<td>50</td>
<td>93</td>
<td>25</td>
</tr>
</tbody>
</table>

EEG = electroencephalography; PPV = positive predictive value; NPV = negative predictive value; diff = difference analysis; ii = interictal; i = ictal.
Ictal SPECT does not always help

- Not helpful if there is clear MTS
  - Increase inpatient cost (some estimates as high as 50% increase)
    - Von Oertzen et al estimated an extra $4000 for a 4 day stay, or an extra $8300/hypothesis generated.
  - Increase length of stay
  - Doubled the risk of secondarily generalized Sz
  - O’Brien showed it can be cost-effective helpful if MRI negative onset

Von Oertzen et al 2011
O’Brien et al 2008
Multiple Injections

- May be needed if -
  - Seizure too short (< 15 sec)
  - Injection too late (>20-30 sec)
  - Not actual typical seizure
  - Secondarily generalized seizure

- Allow > 36 hours between injections to clear tracer
Interictal SPECT is almost always required.
SISCOM can aid in MRI interpretation

Nocturnal hypermotor seizures every night since childhood
Published example of SISCOM highlight a previously MRI-occult dyslasia

Dupont 2013 Epilepsia
Getting the best study

- It takes 10-15 sec for tracer to reach the brain
  - Seizures <15-20 sec may not take up sufficient tracer
- Earlier Injection is Best
  - Preferably < 20 sec by either EEG or clinical onset (whichever comes first)
  - Show the nurse/technician the video and EEG of previously recorded seizures
    - Make sure EEG is visible in room
    - Consider having backup review in EMU control room, with ability to call or alphanumeric page the injection nurse
- Low threshold to inject on patient-reported auras
- Secondarily generalized Seizures?
Early injection is better

<table>
<thead>
<tr>
<th>Injection delay</th>
<th>Correct localization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By visual analysis</td>
</tr>
<tr>
<td>Less than 20 s (n=31)</td>
<td>21 (67.7%)</td>
</tr>
<tr>
<td>More than 20 s (n=50)</td>
<td>26 (52.0%)</td>
</tr>
<tr>
<td>P value</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
2º GTC can be useful (somewhat)

Much less sensitive to focal changes but hemispheric hyperperfusion can support the laterality of seizure onset (80%). Often involves one or more lobes outside the onset zone.

Varghese 2008
Post-ictal perfusion is not helpful

- There are reports of the expected postictal hypoperfusion in zone of onset
- But there are also reports of residual hyper-perfusion
  - Often in surrounding areas, rather than actual onset zone
  - Neurovascular uncoupling

O’Brien 99
Quality Control Hints

- Setting subtraction statistical level
- Always look at raw images as well
  - “reality-check” your SISCOM
  - Are areas of obvious ictal increase not apparent on SISCOM?
  - Is all the signal actually intra-cerebral?
  - Look for corresponding areas of interictal hypoperfusion, although this is less reliable on its own
    - Varghese 2009, McNally 2005
- Sometimes focal areas can only be seen on either raw OR subtracted images (but not both)

Lee & Lee & Yun & Lee & Lee & Lee 2006
Don’t be fooled by signal outside the brain

Ictal

Interictal

“la-la-la”

Screaming and cursing
Look for concordant perfusion changes

- Look for other areas that can be lit up
  - mTLE seizures often also have
    - ipsalateral insula.
  - Basal ganglia (dystonic posturing)
    - Don’t confuse BG signal with orbitofrontal activity
  - Thalamus (uni- or bilateral) in seizures with loss of awareness
- In seizures with prominent motor activity, can often see signal in descending motor pathways
- Contralateral cerebellum

Chassagnon et al 2009

Hippocampal onset post-surgery free patients
Yellow= automatisms
Red= dystonic posturing ± automatisms
Interictal FDG-PET

- Higher spatial resolution than SPECT
- Low temporal resolution
  - FDG-Glucose uptake requires > 20 minutes
- Provides information about interictal metabolism (unless you get lucky & record a seizure during uptake)
  - Should probably include EEG to confirm no seizure during uptake
- Most sensitive for mesiotemporal onset (65 % sensitivity), much less so for extratemporal neocortical seizures (20%)
Interictal FDG-PET – an easy case
FDG-PET

- Areas of hypometabolism often extend outside the epileptogenic zone
- Useful in TLE with normal MRI
  - Can detect 2/3 of depth-electrode confirmed epileptic hippocampi
- Neocortical epilepsy
  - Utility is less consistent
    - Knowlton 2008 found FDG-PET localized ictal focus in 65% of mTLE cases, but only 20% of extratemporal onset cases
Problems with PET

- Averages metabolism over 30-90 minutes
- Can be affected by structural lesions, postictal state
FDG-PET can also show cortical dysfunction that may complement MRI findings.

- PET = MRI lesion
- PET partially overlaps MRI lesion
- PET highlights subtle MRI lesion

Kudr 2013
Comparison MSI vs PET vs SISCOM

- Modalities may be complimentary, depending on the case
- In MRI-normal patients FDG-PET was localizing in 65% of MTLE patients, but only 20% of extra-temporal seizure patients.

<table>
<thead>
<tr>
<th>Diagnostic Value</th>
<th>MSI (CI)</th>
<th>PET (CI)</th>
<th>iSP (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>31% (12.0–46.9)</td>
<td>54% (31.6–66.3)</td>
<td>62% (38.8–74.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>79% (61.2–93.6)</td>
<td>86% (65.0–97.3)</td>
<td>86% (64.6–97.3)</td>
</tr>
<tr>
<td>PPV</td>
<td>57% (22.4–87.2)</td>
<td>78% (45.6–95.8)</td>
<td>80% (50.4–96.2)</td>
</tr>
<tr>
<td>NPV</td>
<td>55% (42.8–65.5)</td>
<td>67% (50.6–75.7)</td>
<td>70.6 (53.2–80.1)</td>
</tr>
</tbody>
</table>

FDG-PET = 2-[18F]fluoro-2-deoxy-d-glucose positron emission tomography; MSI = magnetic source imaging; CI = confidence interval; iSP = ictal single-photon emission computed tomography; PPV = positive predictive value; NPV = negative predictive value.

Spanaki 1999 compared intracranial EEG
Knowlton 2008 compared to surgical outcome
Coregistered MRI/PET can yield to find neocortical lesions
Which Modality

- What are you looking for? Each modality has its own temporal and spatial resolution
  - Epileptic focus
  - Functional Zone
  - Safety of resection
- Need to interpret these findings in comparison to health controls – “what is abnormal?”