Imaging in epilepsy: Ictal perfusion SPECT and SISCOM

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Acquisition

- $^{99m}$Tc-ECD (ethyl cysteinate dimer)
  - $^{99m}$Tc-HMPAO (hexa-methylpropyleneamine oxime) (stabilized form)
- **Tracer trapped in the brain**
  - first pass extraction fraction = 0.61 (Ishizu et al. JNM 1996)
  - lipophilic agent
  - polar metabolite
  - Little washout or regional re-distribution during the first 4 hours
  - %ID: 4-7% ($^{99m}$Tc-ECD) and 2-3% ($^{99m}$Tc-HMPAO) (Catafau JNM 2001)
- **Imaging 1-3 h after tracer injection**
  - Image perfusion - as it was immediately after the injection - at later time points.
  - Reduction of movement artifacts.
- **Unique possibility for ictal imaging!**
Acquisition and reconstruction

SPECT: Single photon emission computed tomography

• Collection of sufficient number of counts (duration versus quality)
• Attenuation correction
• (Scatter correction)
• Typical duration of the scan: ~30 min
• During the acquisition, a sufficient large matrix should be used.
• Iterative reconstruction or filtered backprojection with voxel sizes which are small enough in all directions.
• The same acquisition and reconstruction should be used for the ictal and interictal scan to avoid confounds during the interpretation.
Ictal injection

delivery of 1 GBq $^{99m}$Tc-ECD at 8 a.m. and at noon
(injected dose: 600 - 1000 MBq)
Radiation protection

- Depending on national regulations.
- Shielding of the tracer in the patient room.
- Trained personnel to handle the tracer.
- Radiation exposure to the patient
  - \(^{99m}\)Tc-ECD: 5.7 mSv (adult, typical dose of 740MBq) and largest radiation dose for the bladder wall.
  - \(^{99m}\)Tc-HMPAO: 6.9 mSv (adult, typical dose of 740MBq) and largest radiation dose for the kidneys.
Interictal perfusion SPECT

- **Standardized conditions**
  - At least 15 min before the injection until 10 min thereafter
  - Dimly lit and silent room
  - Supine with eyes closed
  - EEG recording to exclude subclinical epileptic activity

- **Dose**
  - Typical: 740 MBq
  - Note: adapted dose for children!

- **Acquisition, reconstruction and processing**
  - identical to the ictal scan

- **Time between ictal and interictal scan**
  - should be more than 24h (decay of tracer)
  - preferable within a few weeks to make the interpretation easier
Different types of analyses

- **Visual analysis**
  - Assessment of image quality
  - Side-by-side visual assessment
  - Complementary to SISCOM
  - Depends on the experience of the reader

  - Highest sensitivity
  - Best method for use in an individual patient

- **Comparison to a database**
  - SPM: low sensitivity when comparing a single case against a control group
  - ISAS: SPM analysis of the difference image compared to a normal database (McNally et al., Epilepsia 2005; Scheinost et al., Epilepsia 2010)
  - STATISCOM (Kazemi et al. Neurology 2010)

- **Group analysis**
  - SPM: e.g. to assess common changes during specific seizure types and in specific patient populations
SISCOM: the basic steps

- Quality check SPECT and MRI images
  - Coregistration of ictal and interictal SPECT images
    - Quality check coregistration
  - Normalisation of SPECT images
  - Smoothing the SPECT images
  - Subtraction of SPECT images (ictal – interictal) and transformation to a z-score
    - Quality check
  - Coregistration of SPECT images (and the corresponding subtraction) and MRI.
    - Quality check
- Visualisation and interpretation.
Coregistration of ictal and interictal SPECT images

e.g. using mutual information

Before coregistration

After coregistration

Check the coregistration!
Normalisation

- To compensate for differences in injected dose
- To compensate for global changes
  (target = regional relative changes)

By total brain counts
  - Thresholded such that only intracranial voxels are analysed.
  - Use MRI data

By counts in a reference region
  - Cerebellum (but ictal perfusion changes are reported)
  - White matter
  - Pons
Smoothing

• To increase signal to noise
• To increase detectability  (Ghoorun et al. Nucl. Med. Com. 2006)

E.g. with a 3D Gaussian kernel of 12mm FWHM
Subtraction of SPECT images
Transformation to a z-score

• **Subtraction:**
  – Only voxels which are within the measured volume of both SPECT images

• **Transformation to a z-score**
  – histogram calculation
  
  \[ D = \text{‘ictal’} - \text{‘interictal’} \]

  (after normalisation).

  \[ z(i) = \frac{\Delta(i) - \mu}{\sigma} \]

  Voxel i

  \( \mu \) the mean of all brain voxels in D.
  
  \( \sigma \) the standard deviation of all brain voxels in D.

  – Creation of a z-map difference image

**Assumption:** differences are identical and normally distributed in all brain voxels.
Coregistration of SPECT and MRI

Using mutual information

Before coregistration

After coregistration

Check the coregistration!
Coregistration of SPECT and MRI

Using mutual information

Before coregistration

Ictal SPECT

Interictal SPECT

Average SPECT

Transformation

After coregistration

Ω

Coregistration MRI and z-map

Ω
Many techniques for visualisation of the results

Preferable a “dynamic” visualisation in which the z threshold can be changed.
SISCOM: Pitfalls

SISCOM contains:
- seizure onset zone
- Propagation
- normal physiological changes

But also differences in:
- Scanner
- Reconstruction
- Filtering, ...

If epileptic activity is present during the interictal scan, no or very small difference found on SISCOM

Changes due to misregistrations or artifacts in one of the images.

Look also at the individual ictal and interictal SPECT images and the MRI images
• The **largest** and **most intense ictal hyperperfusion** is **not always** representing the **ictal onset zone**.

• Different **perfusion patterns**
Focal dysplastic lesions and perfusion patterns

- Pattern 1 = no propagation (29%)
  - Largest hyperperfusion cluster with highest z-score overlapping with FDL
  - This pattern can be conclusively localised on blinded assessment

CPS, duration: 33 s, injection: 2 s
Focal dysplastic lesions and perfusion patterns

- **Patterns 2 and 3 = propagation (71%)**
  - Largest hyperperfusion cluster with highest z-score at distance from FDL
  - Hourglass pattern
  - These patterns can often not be conclusively localised on blinded assessment

Dupont et al. Epilepsia 2006; 47: 1550-7
An hour glass type pattern in which the least intense lobule represents the ictal onset zone and the most intense hyperperfusion corresponds to propagation of epileptic activity.
Perfusion pattern 3

CPS
duration 46s
Injection 10 s
Interpretation

Always in the context of a full presurgical evaluation

Hyperperfusion clusters

- Ictal injections usually contain the ictal onset zone

- Largest cluster with highest z-score may represent propagated activity and not the ictal onset zone

We need to take into account …
Interpretation

– Injection time
  • the earlier, the better (Van Paesschen et al. Neurology 2000)
  • Injections with a delay < 20s: significant correlation with correct location (Lee et al. Neuroradiology 2006)

– Seizure type and ictal semiology
  • Simple partial seizures: 40% non-localizing
  • Complex partial seizures: best results
  • Secondarily generalized seizures

– Duration of the seizure
  • Transit time of tracer to the brain: around 30 seconds
  • Seizures should last at least 10-15 seconds after injection in order to give localizing information

– Conditions of the ictal injection
  • Interictal injection always in standard conditions
MR-negative epilepsy patients and SISCOM

- Invasive EEG guided by SISCOM

Pitfalls:
- Propagation
- Multifocal seizure onset
“MR-negative” epilepsy patients and SISCOM

- Detection of subtle lesions (FDL) guided by SISCOM
  - Coregistration with MPRAGE and FLAIR (3T MRI)
  - re-evaluation of the MRI guided by the SISCOM revealed small FDL in around 15%

- Advanced image processing of the anatomical MRI will reduce the number of such cases.

sGTCS, duration: 91 s, injection time: 2 s
Summary

Ictal perfusion SPECT

- complementary role in the presurgical evaluation of patients with refractory epilepsy to determine the ictal onset zone (and propagation)
- Role in localization, characterization and guidance of MRI and invasive EEG

- Importance of quality control of the different steps in the analysis
- have a look at the individual ictal and interictal perfusion SPECT images
- SISCOM: interpretation of the pattern and not the search for the biggest or most intense blob
Female, 55 yr, age at onset 38 yr
Ictal injection during a complex partial seizure after = 38s
Duration of the seizure = 73s

Available images:
- Ictal and interictal perfusion SPECT
- MPRAGE

Data are transferred to Analyze7.5 format
- Careful with data conversions. Don’t loose essential information.
- Be careful when using Analyze or Nifti format.
  - E.g. mricro cannot apply nifti transformations.
- Know at all times left and right in the images.
SISCOM: the basic steps

• Mricro/SPM8
  – Quality check SPECT and MRI images
  – Coregistration of ictal and interictal SPECT images
  – Quality check coregistration

• LCN8_subtract
  – Normalisation of SPECT images
  – Smoothing the SPECT images
  – Subtraction of SPECT images (ictal – interictal) and transformation to a z-score

• Mricro/SPM8
  – Quality check
  – Coregistration of SPECT images (and the corresponding subtraction) and MRI.
  – Quality check
  – Visualisation and interpretation.
male, 19 yr, age at onset 10 yr
2 ictal injections
  – during a complex partial seizure after = 35s; duration = 90s
  – during a complex partial seizure after 14s, duration = 68s
Available images:
  – 2 ictal and 1 interictal perfusion SPECT
  – FDG PET
  – MPRAGE
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