Spatial Normalization

- It is important to bear in mind the deep meaning of “Spatial Normalization”:
  - It means the geometrical mapping, voxel by voxel, between subjects.
  - The target is to compare voxel by voxel, the gray matter CBF values between groups.
  - So, we are assuming that we had success in the previous pre-processing steps, realigning, coregistering, fixing the PVE and the atrophy and, finally normalizing.
  - So, as much reliable gray matter CBF voxels we count, much better normalisation.
  - It could be a problem depending on the atrophy degree.

Spatial Normalization: Alternative Routes.

- Normalization can be done to different templates:
  - To MNI
  - Building specific templates.
- When?
  - At the beginning, to MNI and, then, carry out the rest of the post-processing.
  - As a final step, normalizing to MNI the masked gray matter after PVE and Atrophy correction of the CBF.
  - As a final step to generate a CBF template using the gray matter masked CBF.

In the literature we will find different Reference Image for Normalization:

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>PD</th>
<th>EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aslani, 2008</td>
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<td>Alsop, 2008</td>
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<td>Taylor, 2012</td>
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<td>Corzuge, 2012</td>
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<td>Chap, 2010</td>
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<td>Chen, 2011</td>
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<tr>
<td>Johnson, 2006</td>
<td></td>
<td></td>
<td></td>
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<td>Du, 2005</td>
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</tbody>
</table>
Generating a Gray Matter CBF Template with DARTEL

Figure: GM Segmentation + CBF upsampled (GM threshold 0.1)

THE PIPELINED “NIGHTMARE”
**Specific Steps**

Xu, 2010, “Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3.0 T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer’s disease.”

**Specific Steps**

Musiek, 2012, “Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer’s disease.”

**Specific Steps**

Specific Steps
Asllani 2008, "Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer’s disease"

Specific Steps
Asllani 2008, "Regression Algorithm Correcting for Partial Volume Effects in Arterial Spin Labeling MRI"

Specific Steps
Taylor 2012, "Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study"
Specific Steps
Doyle, 2013, “Multivariate decoding of brain images using ordinal regression”

Specific Steps
Corouge, 2012, “Arterial Spin Labelling at 3T in semantic dementia: perfusion abnormalities detection and comparison with FDG-PET”

Specific Steps
Chao, 2010, “ASL Perfusion MRI Predicts Cognitive Decline and Conversion From MCI to Dementia”
Specific Steps
Johnson, 2005, "Pattern of Cerebral Hypoperfusion in Alzheimer Disease and Mild Cognitive Impairment Measured with Arterial Spin-labeling MR 1 Imaging: Initial Experience"

- **CORREGISTER**
  - Control and Label to PD
- **CORREGISTER**
  - PD to T1 moving Control and Label
- **COMPUTE**
  - CBF
- **CORRECT**
  - For gain and coil loading

- **NORMALIZE**
  - CBF to Mean CBF from all images
- **MASK**
  - CBF (GAMMA)
- **PYE & MASK**
  - $\text{CBF} = \text{CBF}_{\text{GM}} > 0.2 + 0.4 \times \text{P}_\text{GM} > 0.3 + 0.2 \times \text{P}_\text{WM} > 0.2$

- **NORMALIZE**
  - T1 specific Template
- **DEMIC**
  - Negative and +2SD

COST AID STSM
- **ASL Toolbox**
  - www.fundacioncien.es/areas/asl_toolbox.asp
- **Virginia Mato(QSF) & Fernando Zelaya(IOP)**

Developed during a Short Term Scientific Mission (STSM) collaborating:
- Department of Neuroimaging, IoP, King's College London (Fernando Zelaya)
- Laboratory of Neuroaging of CIEN Foundation, Reina Sofia Foundation and Rey Juan Carlos University (Virginia Mato, Juan A. Hernández Tamames).

Includes all the steps needed for preparing the CBF maps for a statistical analysis.

Is written in MATLAB with different analysis strategies depending on the ASL image readout and the type of structural scans available from each subject (T2-weighted and/or T1-weighted high-resolution scans).
Basic steps:
- Co-registration of the CBF map to the structural scan
- Skull-stripping of the co-registered CBF map
- Normalization of the structural scan and co-registered and skull-stripped CBF map to the MNI space
- Smoothing of the final, spatially normalized CBF

Modes:
- Upsampling CBF to T1/T2
- Downsampling T1/T2 to CBF
**SPM8 — Specify 2nd level**

**Options** represent ways of defining the design matrix, \( X \), e.g.:
- One sample t-test: \( X = \)
- Two sample t-test: \( X = \)
- ANOVA
- Full factorial
- Flexible factorial
- Linear regression
- etc.

**Confounding variables and Co-Variables.**

- Age
- Gender
- Haematocrit (related to brightness value) Lower Haematocrit higher CBF.
- Intra-subject brightness mean value. (Not applicable if corrected previously)
- Ratio between intra-subject bright mean value vs overall mean value (all subjects mean). Not recommendable if we are expecting a difference in the global mean value between groups.
- Intrasubject gray matter volume (it does not make sense if you have previously corrected atrophy)
- Key Idea: If you are not sure about how important is one confounding then try to use "F-Contrast".

**Fixed and Random Effects**

- Fixed effect is the common choice
- Random is applicable in multi-site acquisitions when are mixing the subjects from different sites
Fixed effects vs Random effects

- **Fixed effects**
  - Controlled and of interest
  - Does not take into account within subject variability
  - Allows drawing conclusions about the sample

- **Random effects**
  - Random sampled from a larger population
  - Takes into account within and between subject variability
  - Allows drawing conclusions about the population

Group comparison

- Fixed effects model:
  \[ y_{ai} = b_a + e_{ai} \]
  \[ y_{ci} = b_c + e_{ci} \]

\[
\begin{bmatrix}
Y_{a1} \\
\vdots \\
Y_{a10} \\
Y_{c1} \\
\vdots \\
Y_{c10}
\end{bmatrix} =
\begin{bmatrix}
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1
\end{bmatrix}
(\begin{bmatrix} b_a \\ b_c \end{bmatrix})
+ \begin{bmatrix} e_{a1} \\
\vdots \\
e_{a10} \\
e_{c1} \\
\vdots \\
e_{c10} \end{bmatrix} \]

Fixed effects vs Mixed effects model

- **Fixed effects model**:
  \[ Y = X\beta + \varepsilon, \quad \varepsilon \sim N(0,\sigma_w) \]

- **Mixed effects model**:
  \[ Y = X\beta + Z\eta + \varepsilon, \quad \eta \sim N(0,\sigma_b), \quad \varepsilon \sim N(0,\sigma_w) \]

Random effect between group within subject
**Group comparison**

- Mixed effects model:
  
  \[ y_{ai} = b_1 + u_a + \varepsilon_{ai} \]
  
  \[ y_{ci} = b_2 + u_c + \varepsilon_{ci} \]

\[
\begin{pmatrix}
  b_0 \\
  b_1 \\
  b_2 \\
  u_a \\
  u_c
\end{pmatrix} =
\begin{pmatrix}
  1 & 0 \\
  0 & 1
\end{pmatrix}
\begin{pmatrix}
  b_a \\
  b_c
\end{pmatrix} +
\begin{pmatrix}
  \varepsilon_{a1} \\
  \varepsilon_{a10} \\
  \varepsilon_{c1} \\
  \varepsilon_{c10}
\end{pmatrix}
\]

**Mixed effects model**

Mixed effects model:

\[ Y = X\beta + Z\eta + \varepsilon, \quad \eta \sim N(0, \sigma^2_\eta) \quad \varepsilon \sim N(0, \sigma^2_w) \]

Mixed effects model (two stages):

Stage 1: \[ Y = X\beta + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2_w) \]

Stage 2: \[ \beta = X_i\beta + \eta, \quad \eta \sim N(0, \sigma^2_\beta) \]

**Some Examples at QSF**
Male  Female
Negative correlation of HCT% vs CBF in Posterior Cingulate


Whole brain dependence of CBF with HCT%

Results

Posterior Cingulate

• García-Polo P; “Comparison of neuroimaging biomarkers in Alzheimer’s disease” ISMRM 2013; Salt Lake City, Utah, U.S.A.
Results Control vs MCI-M

No Corr p<0.0005 k=50vox
PET_corr p<0.0005 k=50vox

Asllani p<0.0005 k=50vox

GM Atrophy p<0.05
Precuneus
Red: Atrophy (Asllani)
Green: Hypoperfusion

Hippocampus
Red: Atrophy (Asllani)
Green: Hypoperfusion

Summary: Main Issues in Data Preparation for Group Comparison in ASL
- Realignment: Control & Labeled
- Intra-Corregistration: if Upsampling, Interpolation using Nearest Neighbour, not splines.
- Global Perfusion Quantification
- Bright Normalization: Haematocrit, Gain, Coil loading
- Normalization. Alternative routes and reference images
- Statistics: confounding variables, Fixed or Random Effects
References & General Steps I

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- Andrews Gemelli et al., ALE co-registration T2g, Calculate delta MR, Calculate Perfusion, Normalise T2 to MNI and new CBF
- Allison et al., 2006, ICBFM
- Matic et al., Corregitration ALE, T1, T2, Normalise T1 to MNI and new CBF
  - Correction of M0, M1, M2, CBF correction for gas and pulsating a, PVE Correction to subtraction of M0, CBF contribution and spatially corrected, T1 to anatomical T1, Normalise T2 to MNI, template
- Corregitration I et al., 2013, P3E3FM
  - Correction of M1, T1, T2, Calculated T1, M0 Correction (manual), Normalise T1 to MNI, new CBF, CBF intensity Normalise
- Johnstone et al., 2009, Rehology
- Correction of M0, T1, T2, Corregitration ALE, M0 and M1, M2, Correction T1, T2, Calculated T1, CBF correction to gas and pulsating a, PVE Correction to subtraction of M0, CBF contribution and spatially corrected, T1 to anatomical T1, Normalise T2 to MNI (manual), T2 to MNI, template
- Parker et al., 2004, NMR
  - Corregitration T1, T2, ALE Compartment Models for PVE correction, Normalise data to a sub-dwelted perfusion weighted images for MNI (Gamma template) using CBF, Smooth

General Steps II

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- Xu D et al., 2004, NMR Brain
- Xu C et al., 2005, NMR Brain
- Allinson et al., 2006, NMR Brain
- Emile Marot et al., 2008, verified by a, M1, M2 and T2, To compenated with M1, Mask after removing a, 3D affine
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  - Correction of M1, correction of M2, correction of T1, correction of T2, Correction of M0, Correction of M1, Correction of M2, Correction of T1, Correction of T2, Correction of M0, Correction of M1, Correction of M2
- Duch et al., 2008, Neuroimage
  - Correction of M1, correction of M2, correction of T1, correction of T2, Correction of M0, Correction of M1, Correction of M2, Correction of T1, Correction of T2, Correction of M0, Correction of M1, Correction of M2
- Doyle et al., 2010, Neuroimage
  - Correction of M1, correction of M2, correction of T1, correction of T2, Correction of M0, Correction of M1, Correction of M2, Correction of T1, Correction of T2, Correction of M0, Correction of M1, Correction of M2

05/07/13