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.

46

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 mater after PVE and Atrophy correction of the CBF.
  - As a final step to generate a CBF template using the gray matter masked CBF

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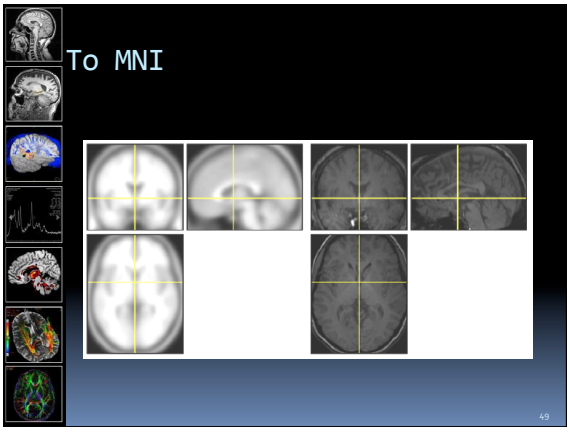
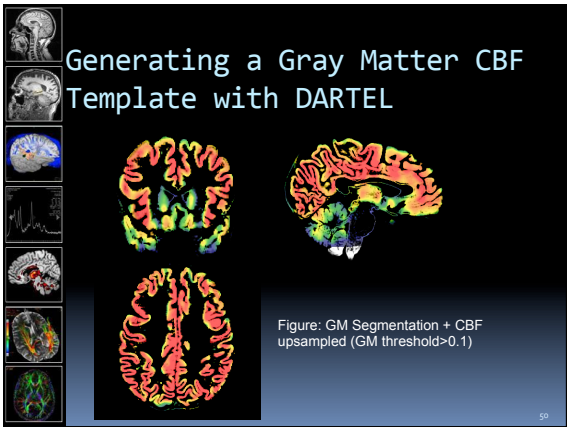
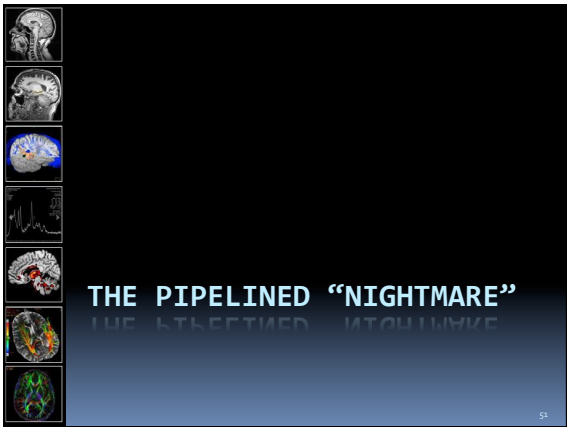
In the literature we will find different Reference Image for Normalization:

T1	T2	PD	EPI
Musiek, 2012	Doyle, 2013	Xu, 2010	Parkes, 2004
Asllani, 2008		Alsop, 2008	
Taylor, 2012			
Corouge, 2012			
Chao, 2010			
Chen, 2011			
Johnson, 2006			
Du, 2005			

48

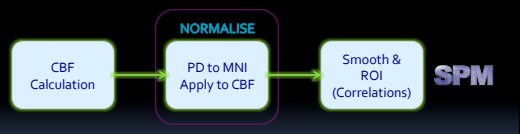

To MNI
49


Generating a Gray Matter CBF Template with DARTEL
Figure: GM Segmentation + CBF upsampled (GM threshold>0.1)
50


THE PIPELINED "NIGHTMARE"
51

Specific Steps

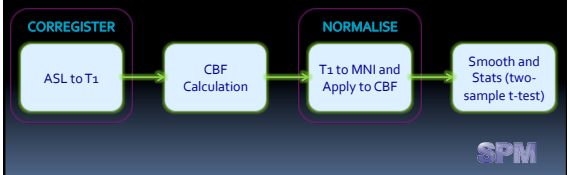
Xu, 2010, "Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3.0 T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer's disease"



52

Specific Steps

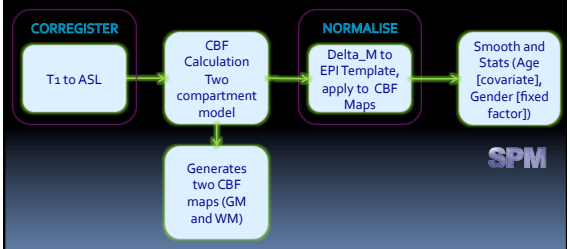
Musiek, 2012, "Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease"



53

Specific Steps

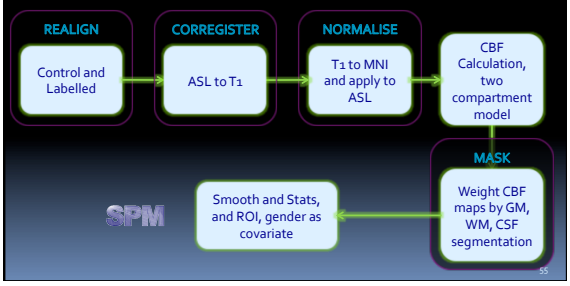
Parkes, 2004, "Normal Cerebral Perfusion Measurements Using Arterial Spin Labeling: Reproducibility, Stability, and Age and Gender Effects"



54

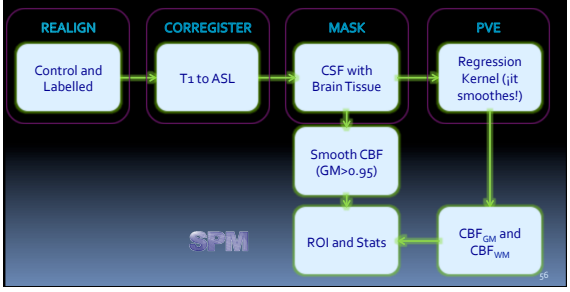
Specific Steps

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



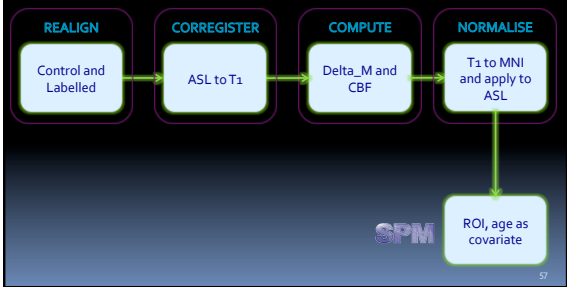
Specific Steps

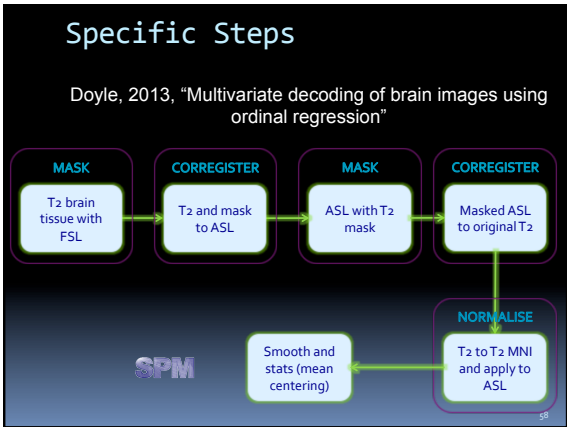
Asllani, 2008, "Regression Algorithm Correcting for Partial Volume Effects in Arterial Spin Labeling MRI"

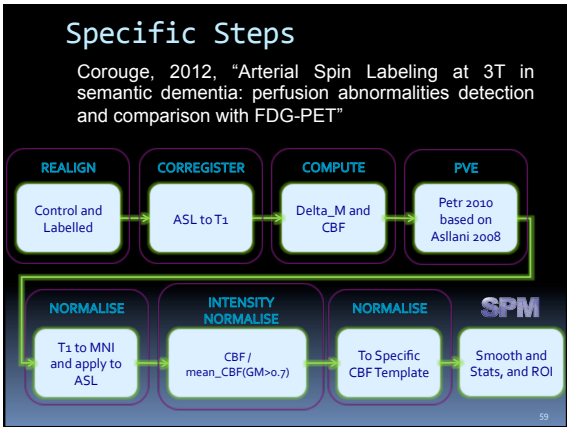


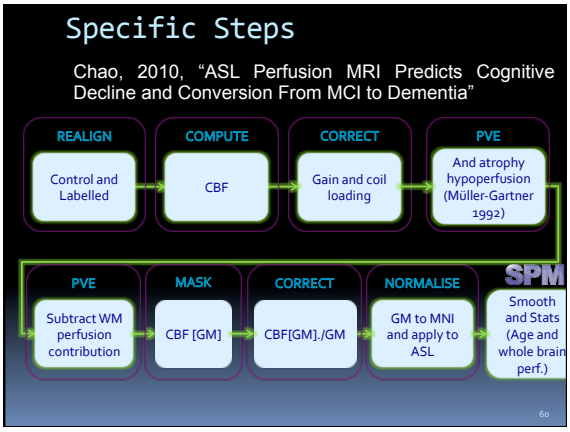
Specific Steps

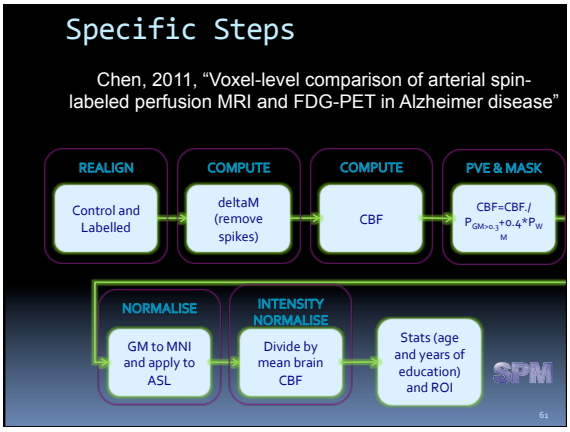
Taylor, 2012, "Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study"

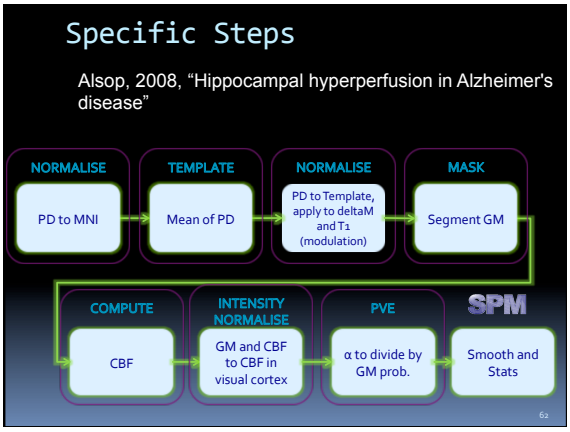


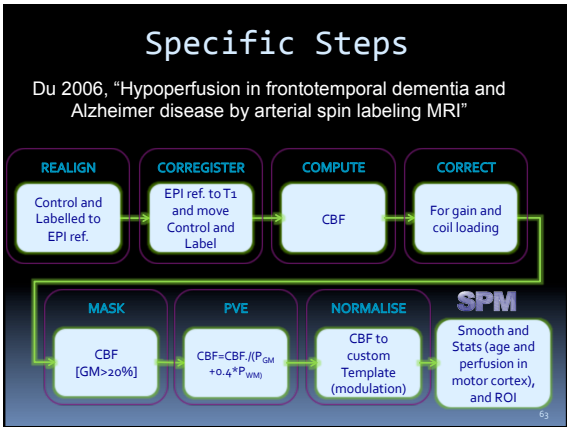

Specific Steps
Doyle, 2013, "Multivariate decoding of brain images using ordinal regression"
MASK
T2 brain tissue with FSL
CORREGISTER
T2 and mask to ASL
MASK
ASL with T2 mask
CORREGISTER
Masked ASL to original T2
NORMALISE
T2 to T2 MNI and apply to ASL
Smooth and stats (mean centering)
SPM
58

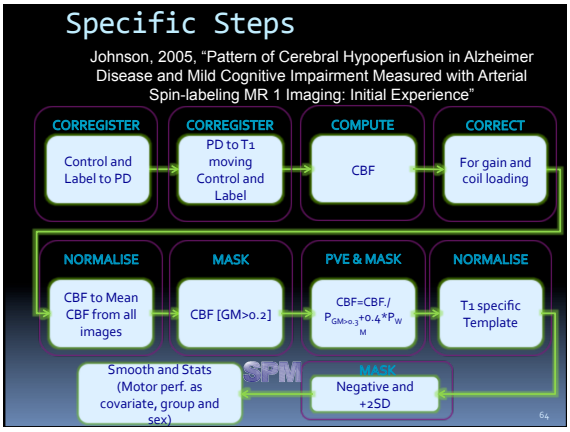

Specific Steps
Corouge, 2012, "Arterial Spin Labeling at 3T in semantic dementia: perfusion abnormalities detection and comparison with FDG-PET"
REALIGN
Control and Labelled
CORREGISTER
ASL to T1
COMPUTE
Delta_M and CBF
PVE
Petr 2010 based on Asllani 2008
NORMALISE
T1 to MNI and apply to ASL
INTENSITY NORMALISE
CBF / mean_CBF(GM>0.7)
NORMALISE
To Specific CBF Template
SPM
Smooth and Stats, and ROI
59

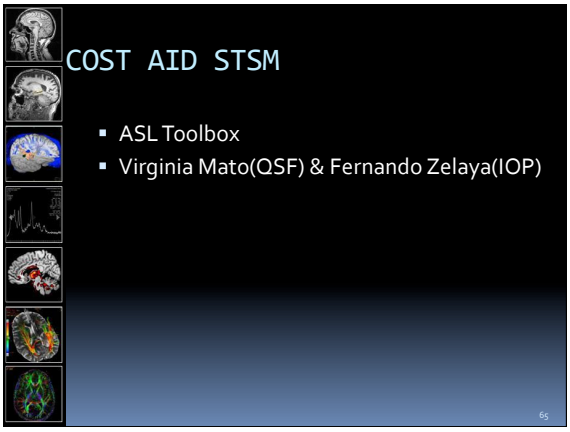

Specific Steps
Chao, 2010, "ASL Perfusion MRI Predicts Cognitive Decline and Conversion From MCI to Dementia"
REALIGN
Control and Labelled
COMPUTE
CBF
CORRECT
Gain and coil loading
PVE
And atrophy hypoperfusion (Müller-Gartner 1992)
PVE
Subtract WM perfusion contribution
MASK
CBF [GM]
CORRECT
CBF[GM]./GM
NORMALISE
GM to MNI and apply to ASL
SPM
Smooth and Stats (Age and whole brain perf.)
60

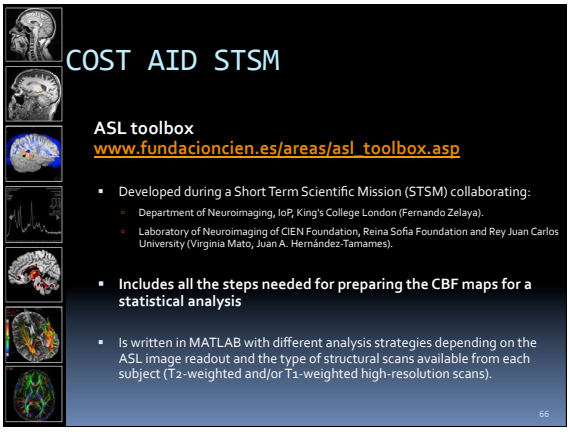

Specific Steps
Chen, 2011, "Voxel-level comparison of arterial spin-labeled perfusion MRI and FDG-PET in Alzheimer disease"
REALIGN
Control and Labelled
COMPUTE
deltaM (remove spikes)
COMPUTE
CBF
PVE & MASK
CBF=CBF./ $P_{GM>0.3}$+0.4*P_{WM}
NORMALISE
GM to MNI and apply to ASL
INTENSITY NORMALISE
Divide by mean brain CBF
Stats (age and years of education) and ROI
SPM
61


Specific Steps
Alsop, 2008, "Hippocampal hyperperfusion in Alzheimer's disease"
NORMALISE
PD to MNI
TEMPLATE
Mean of PD
NORMALISE
PD to Template, apply to deltaM and T1 (modulation)
MASK
Segment GM
COMPUTE
CBF
INTENSITY NORMALISE
GM and CBF to CBF in visual cortex
PVE
α to divide by GM prob.
SPM
Smooth and Stats
62


Specific Steps
Du 2006, "Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI"
REALIGN
Control and Labelled to EPI ref.
CORREGISTER
EPI ref. to T1 and move Control and Label
COMPUTE
CBF
CORRECT
For gain and coil loading
MASK
CBF [GM>20%]
PVE
CBF=CBF./(P_{GM} +0.4*P_{WM})
NORMALISE
CBF to custom Template (modulation)
SPM
Smooth and Stats (age and perfusion in motor cortex), and ROI
63


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
NORMALISE
CBF to Mean CBF from all images
MASK
CBF [GM>0.2]
PVE & MASK
CBF=CBF./ P_GM>0.3+0.4*P_WM
NORMALISE
T1 specific Template
MASK
Negative and +2SD
SPM
Smooth and Stats (Motor perf. as covariate, group and sex)
64


COST AID STSM
ASL Toolbox
Virginia Mato(QSF) & Fernando Zelaya(IOP)
65


COST AID STSM
ASL toolbox
www.fundacioncien.es/areas/asl_toolbox.asp
Developed during a Short Term Scientific Mission (STSM) collaborating:
Department of Neuroimaging, IoP, King's College London (Fernando Zelaya).
Laboratory of Neuroimaging 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).
66

GUI software analysis

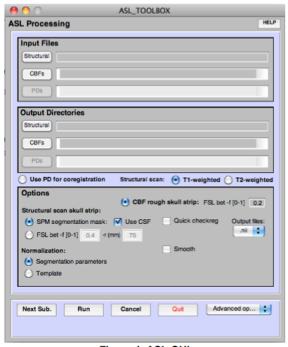


Figure 1. ASL GUI

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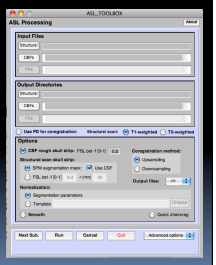
Basic steps:

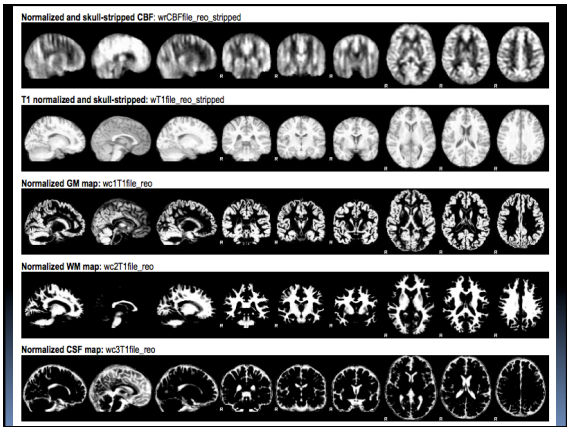
- Co-registration of the CBF map to the structural scan
- Skull-stripping of the co-registered CBF map
- Normalization of the structural scan and co-registered and skull-stripped CBF map to the MNI space.
- Smoothing of the final, spatially normalised CBF



Modes:

- Upsampling CBF to T1/T2
- Downsampling T1/T2 to CBF

68



ROI GUI offers extraction of CBF values from anatomically or functionally defined Regions of Interest

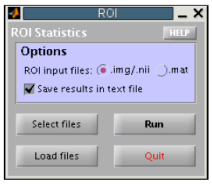
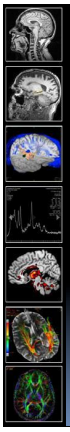


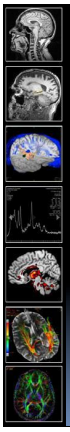
Figure 2. ROI GUI

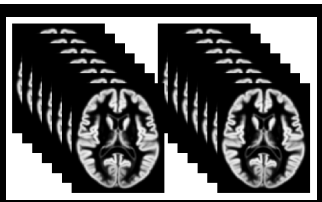
70

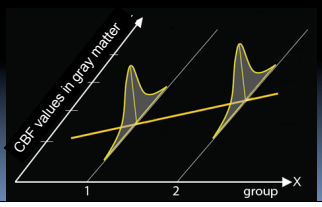


Stats

71







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SPM8 – Specify 2nd level

Find several options:

- One sample t-test
- Two sample t-test
- ANOVA
- Full factorial
- Flex factorial
- Linear regression
- etc.

Options represent ways of defining the design matrix, X, e.g.:

- One sample t-test: X =
- Two sample t-test: X =
- Full factorial: X =
- Linear regression: each column of X is one user defined variable.
- Flex factorial: like full factorial without including all interactions

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Confounding variables and Co-Variables.

- Age
- Gender
- Haematocrit (related to brightness value) Lower Haematrocrit higher CBF.
- Intra-subject brightness mean value. (Not applicable if corrected previously)
- Ratio between intrasubject 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".

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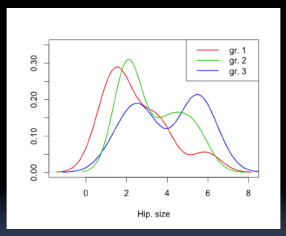
Fixed and Random Effects



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

75

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

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Group comparison

- Fixed effects model:

$$y_{ai} = b_a + e_{ai}$$
$$y_{ci} = b_c + e_{ci}$$

$$\begin{bmatrix} y_{a1} \\ \vdots \\ y_{a10} \\ y_{c1} \\ \vdots \\ y_{c10} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{pmatrix} b_a \\ b_c \end{pmatrix} + \begin{bmatrix} e_{a1} \\ \vdots \\ e_{a10} \\ e_{c1} \\ \vdots \\ e_{c10} \end{bmatrix}$$

77

Fixed effects vs Mixed effects model

Fixed effects model:

$$Y = X\beta + \varepsilon, \qquad \varepsilon \sim N(0,\sigma_w)$$

Mixed effects model:

$$Y = X\beta + Z\eta + \varepsilon, \qquad \eta \sim N(0,\sigma_b) \quad \varepsilon \sim N(0,\sigma_w)$$

Random effect — between group — within subject

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Group comparison

- Mixed effects model:

$$y_{ai} = b_1 + u_a + e_{ai}$$
$$y_{ci} = b_2 + u_c + e_{ci}$$

$$\begin{pmatrix} b_a \\ b_c \end{pmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} + \begin{bmatrix} u_a \\ u_c \end{bmatrix}$$

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Mixed effects model

Mixed effects model:

$Y = X\beta + Z\eta + \varepsilon, \quad \eta \sim N(0,\sigma_b) \quad \varepsilon \sim N(0,\sigma_w)$

Mixed effects model (two stages):

Stage 1: $Y = X\beta + \varepsilon, \quad \varepsilon \sim N(0,\sigma_w)$

Stage 2: $\beta = X_g\beta_g + \eta, \quad \eta \sim N(0,\sigma_b)$

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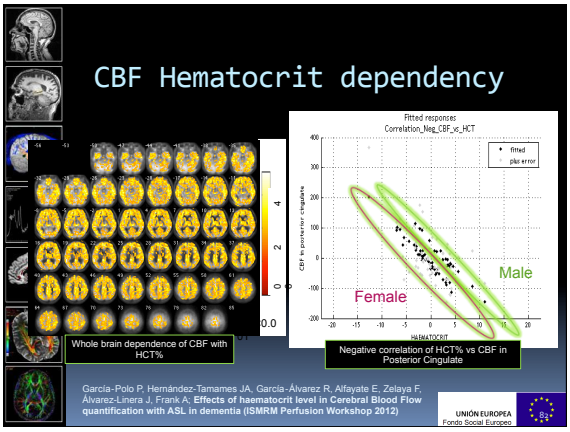
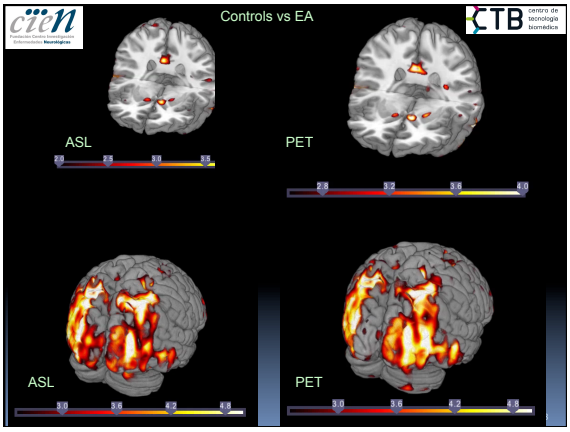
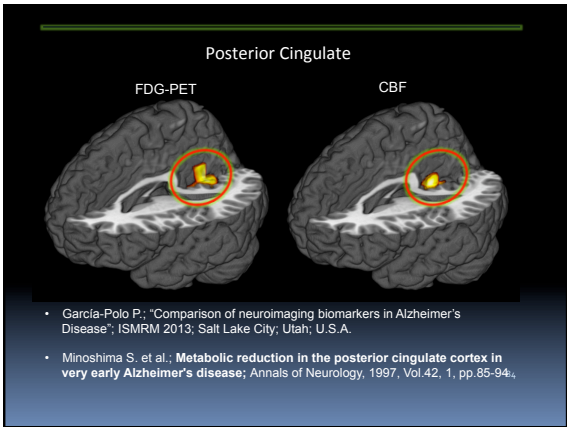
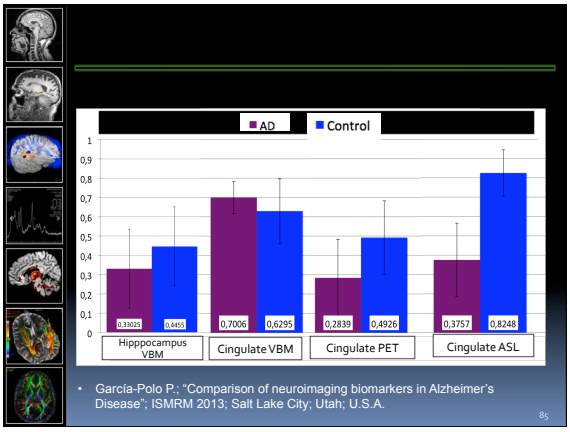
Some Examples at QSF

81


CBF Hematocrit dependency
Fitted responses
Correlation_Neg_CBF_vs_HCT
fitted
plot error
Male
Female
Whole brain dependence of CBF with HCT%
Negative correlation of HCT% vs CBF in Posterior Cingulate
García-Polo P, Hernández-Tamames JA, García-Álvarez R, Alfayate E, Zelaya F, Álvarez-Linera J, Frank A; Effects of haematocrit level in Cerebral Blood Flow quantification with ASL in dementia (ISMRM Perfusion Workshop 2012)
UNIÓN EUROPEA
Fondo Social Europeo

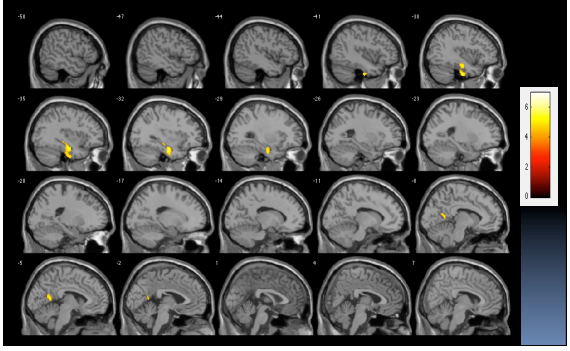

Controls vs EA
CTB
ASL
PET
ASL
PET

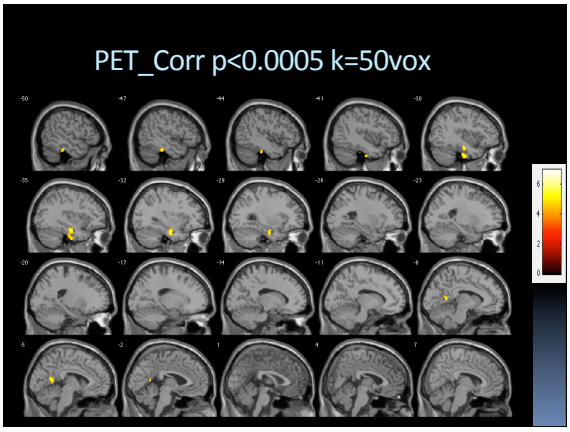

Posterior Cingulate
FDG-PET
CBF
García-Polo P.; "Comparison of neuroimaging biomarkers in Alzheimer's Disease"; ISMRM 2013; Salt Lake City; Utah; U.S.A.
Minoshima S. et al.; Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease; Annals of Neurology, 1997, Vol.42, 1, pp.85-94

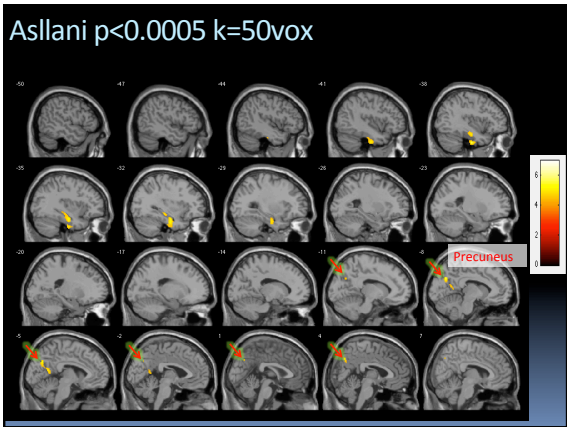


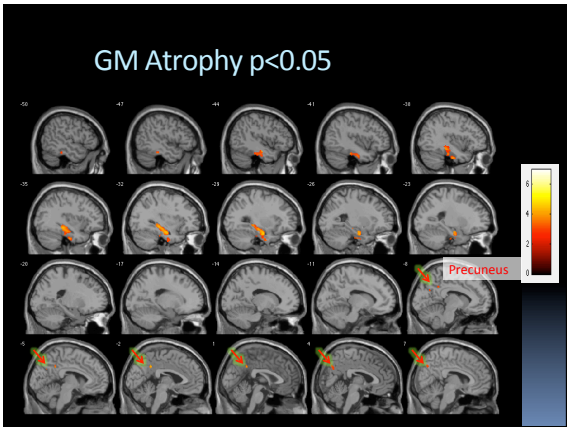
Results Control vs MCI-M

No Corr p<0.0005 k=50vox



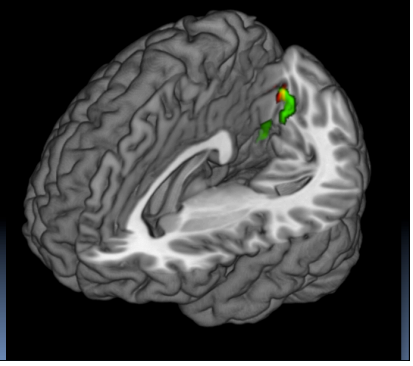

PET_Corr p<0.0005 k=50vox


Asllani p<0.0005 k=50vox
Precuneus


GM Atrophy p<0.05
Precuneus

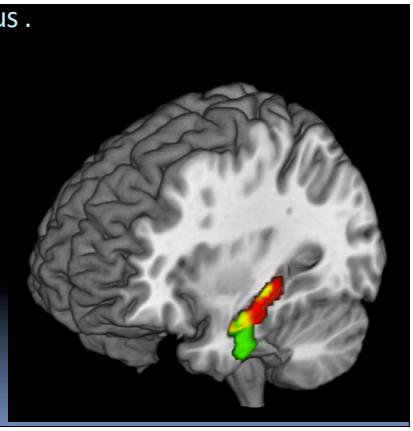
Precuneus

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

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References & General Steps I

- Taylor J.P. et al.; 2012; BJPsych
  - 1. Motion Correction, Mc, MI 2. ASL co-registered to T1 3. Calculate delta M 4. Calculate Perfusion 5. Normalise T1 to MNI and move CBF
- Asllani I. et al.; 2008; JCBFM
  - 1. Motion Correction Mc, MI 2. Corregister ASL to T1 3. Normalise T1 to MNI and move CBF
- Chao L.L. et al.; 2010; Alz. Dis. Assoc. Disord.
  - 1. Corregistration Mc, MI 2. Calculate CBF 3. CBF Correction for gain and coil loading 4. PVE Correction (subtraction of WM CBF contribution and atrophy correction, T1 downsampled to CBF) 5. Normalise to T1 specific template
- Corouge I. et al, 2012; INSERM
  - 1. Corregistration Mc, MI 2. . Corregister ASL to T1 3. Calculate CBF 4. PVE Correction (Asllani) 5. Normalise T1 to MNI and move CBF 6. CBF Intensity Normalise
- Johnson N. A. et al. ; 2005; Radiology
  - 1. Corregistration CBF to T1 2. Corregistration Mc and MI to Mo 3. Corregitration (2) to T1 3. Calcultate CBF 4. CBF Correction for gain and coil loading 5. CBF Intensity Normalise 6. GM mask in CBF space (>0.2) 7. PVE CBF=CBF/(Pgm+0.4*Pwm) 8. Normalise to T1 specific template (AD + CN) 8. Negative CBF values and ±SD out
- Parkes L. M. et al.; 2004; MRM
  - 1. Corregistration T1 to CBF 2. Two Compartment Model for PVE correction 3. Normalise deltaM or unsubtracted perfusion weighted images to MNI (EPI template) moving CBF 4. Smooth

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General Steps II

- Musiek E. S. et al.; 2012; Alzheimer's and Dementia
  - 1. Corregistration Mc, MI 2. CBF Calcultation 3. Normalise to MNI PET
- Xu G. et al.; 2010; NMR Biomed
  - 1. Compute CBF maps 2. Normalise PD to MNI and move CBF 3. ROI
- Asllani I. et al.; 2008, MRM
  - 1. Realign Mc and MI 2. T1 segment GM, WM and CSF 3. T1 corregistered to first Mc 4. Mask of brain tissue. 5. ROI
- Alsop D. C. et al.; 2008; Neuroimage
  - 1. Normalise PD to MNI 2. Mean of PD as Template 3. Normalise to Template_PD PD, deltaM (modulation) and T1 4. Segment T1 and mask PD 5. Compute CBF maps 5. Normalise GM and CBF maps to ROI in visual cortex. 6. PVE correction
- Chen et al.; 2011; Neurology
  - 1. Corregister Mc and MI to T1 2. Compute Mc-MI (remove spikes from motion artifacts) 3. Compute CBF 4. PVE (CBF=CBF/Pgm(>0.3)+0.4*Pwm) in low res 5. Normalise GM to MNI and move CBF_Corr 6. Normalise CBF by mean_brain_CBF
- Du A.T. et al.; 2006; Neurology
  - 1. Corregister Mc and MI to EPI reference 2. Corregister EPI to T1 and move Mc and MI 3. Compute CBF 4. Correct for Coil Loading 5. GM WM and CSF segmentations and custom template 6. GM downsample to CBF and mask >20% 7. PVE CBF=CBF/(Pgm+0.4*Pwm) 8. Normalise CBF corrected to custom Template (with modulation to account for atrophy)
- Doyle O.M. et al.; 2013; Neuroimage
  - 1. BET T2 with FSL 2. Corregister T2 and mask to ASL 3. Mask ASL with brainmask from T2 and corregister ASL to original T2 4. Normalise T2 to T2 MNI template and move ASL 5. Smooth and stats with mean centering

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