2024 KHBM Winter School
OHBM Korea Chapter Program

Statistical Parametric Mapping (SPM) for Voxel-Based Morphometry & PET analysis

Introduction to Principles

Chongwon Pae, Ph.D.
paecw@chauniv.ac.kr

Department of Psychiatry
CHA Bundang Medical Center
CHA University School of Medicine

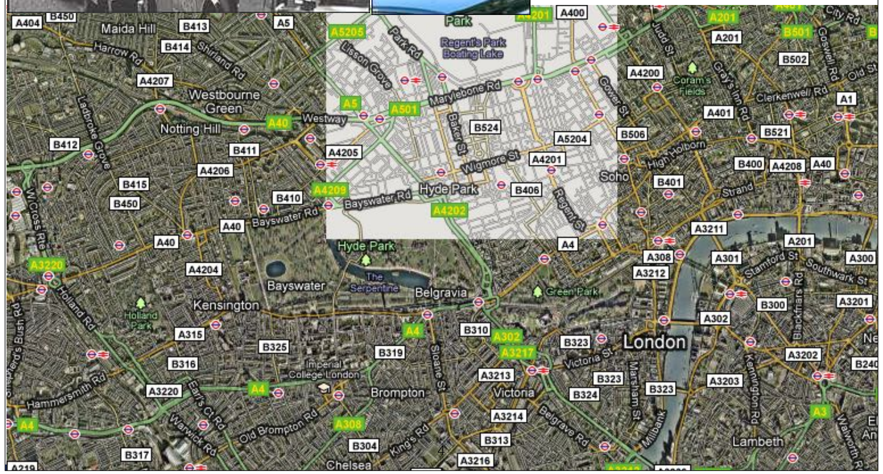
Table of Contents

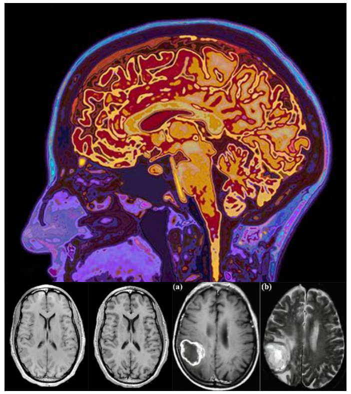
This presentation includes materials from various sources, especially, UCL SPM lecture materials from http://www.fil.ion.ucl.ac.uk/spm/

Navigation-related structural change in the hippocampi of taxi drivers

Maguire E A et al. PNAS 2000;97:4398-4403

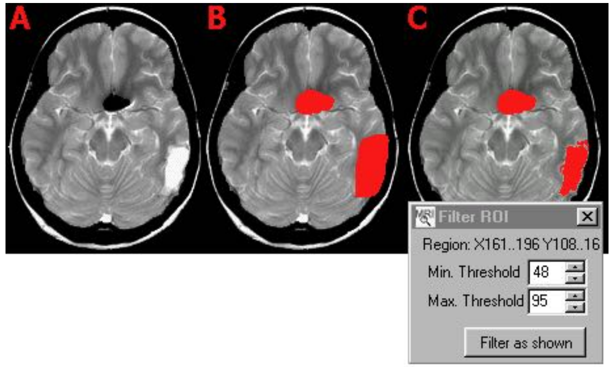
Citation: 4300+ times (2024)



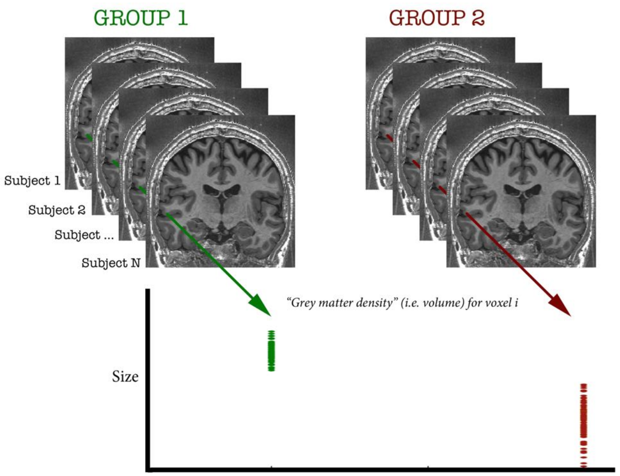


How can we analyze brain differences based on its structure?

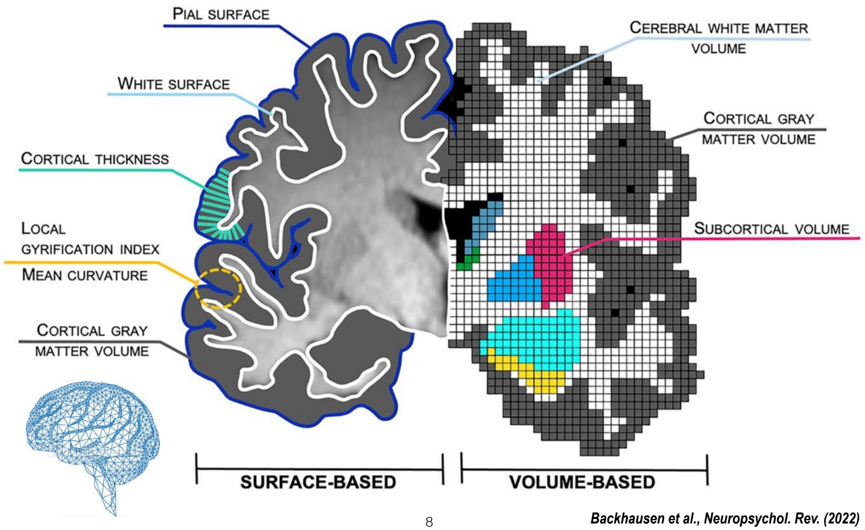
Region-of-Interest (ROI) Approach



Voxel Based Approach

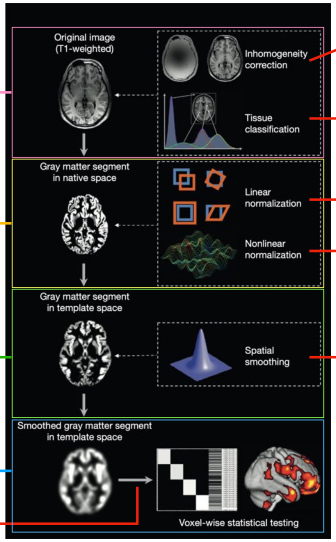


Analysis of structural MRI



Backhausen et al., Neuropsychol. Rev. (2022)

VBM: An Overview



Tissue Classification
The part we're interested in is gray matter.

Spatial Normalization
Spatially normalized to match a comon template

Spatial Smoothing
Smoothed with an isotropic Gaussian kernel

Statistical Inference
Entered into a statistical model

Corrects image intensity distortion caused by magnetic field imbalance in MRI scans.

Gray matter, white matter, cerebrospinal fluid.

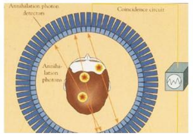
Rigid body transformation (DOF=6)
Affine transformation (DOF=12)

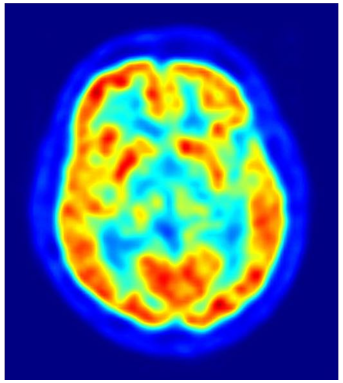
Non-linear transformation

An isotropic Gaussian kernel

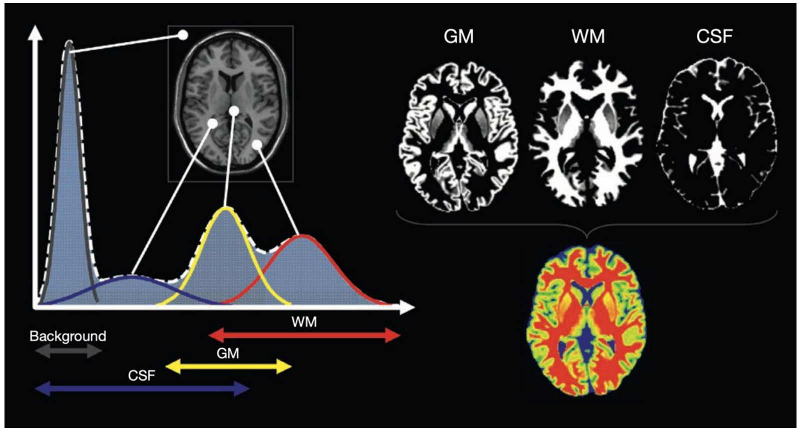
Principles of PET

- A tracer (radionuclide) emits a positron, which annihilates with an electron, emitting a pair of gamma rays in opposite directions
- The detected lines can be grouped into projection images (sinograms) and reconstructed into tomographic images
- Different tracers allow various properties to be measured
  - 15O can measure blood flow relatively quickly (<1 min) but requires a cyclotron because of its short 2 minute half-life
  - 18F Fluorodeoxyglucose (FDG) measures glucose metabolism, and has a half life of 110 minutes
  - Other tracers exist that bind to interesting receptors (e.g. dopamine, serotonin) or beta-amyloid plaques





Tissue Classification



Spatial Normalization

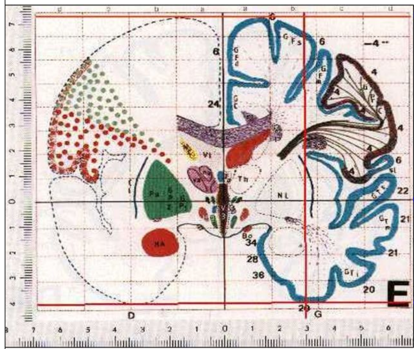
- Individual brains need to undergo spatial normalization to ensure voxel-wise comparability
- Spatial normalization includes linear and nonlinear transformations
  - Linear transformation: translation, rotation, scaling, sheering
  - Nonlinear transformation
- Despite these transformations, a perfect match between any two brains is improbable due to unique local anatomies
- Additional processes are often required for a more accurate comparison (e.g., Jacovian determinants)

Spatial Normalization

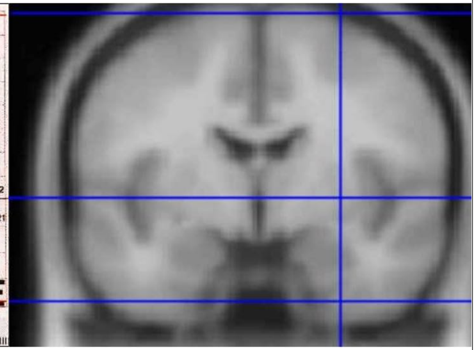
- To analyze our data, we need to accurately align identical structures voxel wise
- To do this, we calculate the transformation to a “Template space”
- Calculating these transformations (warps) also encodes regional information about the amount of compression or expansion required compared to the average – Which are used for VBM
- VBM is crucially dependent on registration performance
- The Shoot (& DARTEL) toolbox combines several methodological advances to address these limitations

Standardized spaces

The Talairach Atlas



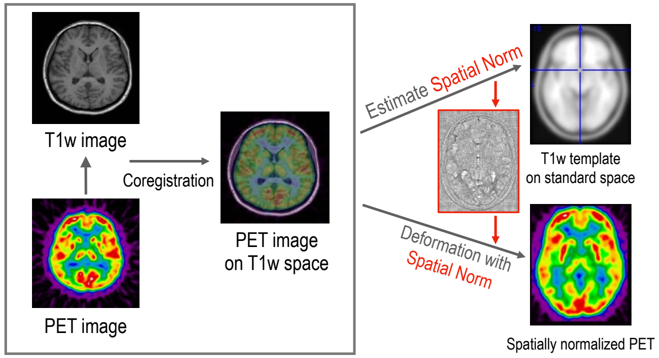
The MNI/ICBM AVG152 Template



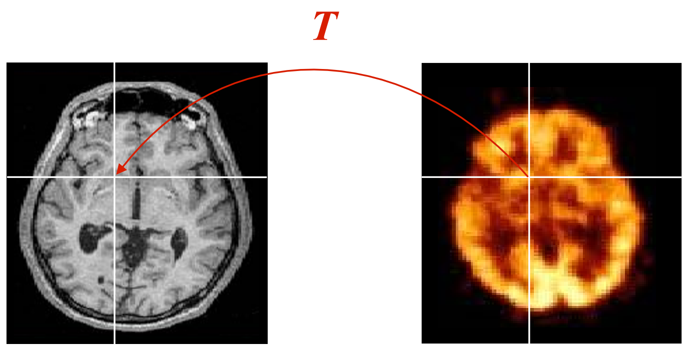
The MNI template follows the *convention* of T&T, but doesn’t match the *particular brain*

Recommended reading: http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach

Pipeline of spatial normalization of PET



Registration? Transformation!

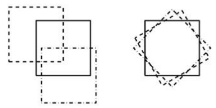


Reference (target) image

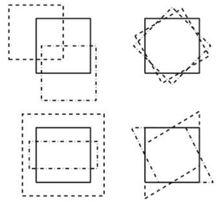
Source image

Transformation

- Linear transformation
  - Rigid body transformation (DOF=6)
  - Affine transformation (DOF=12)
- Non-linear transformation



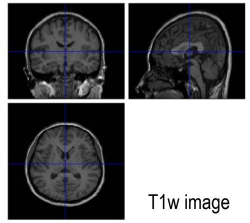
Rigid body transformation



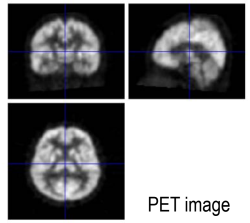
2D Affine transformation

Coregistration

- Inter-modal registration
- Match images from same subject but different modalities
  - anatomical localization of single subject activations
  - achieve more precise spatial normalization of functional image using anatomical image
- Assumes no shape change, and motion is **rigid-body**

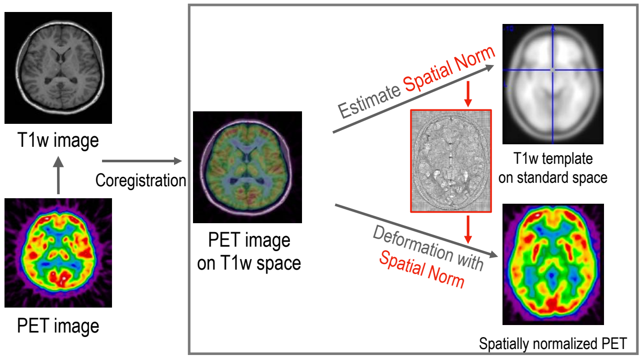


T1w image

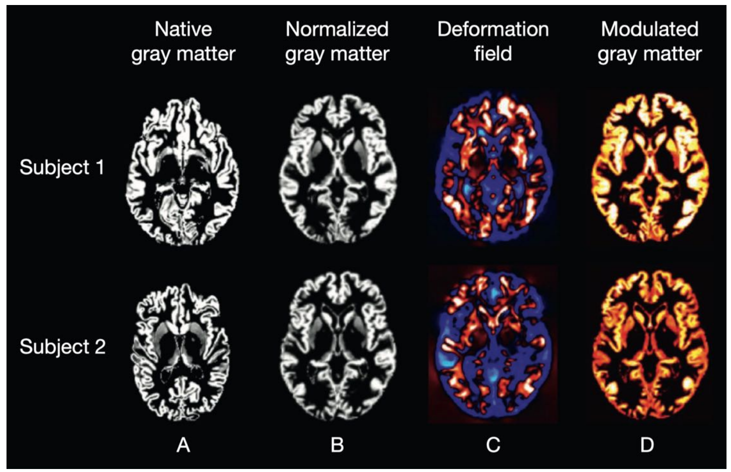


PET image

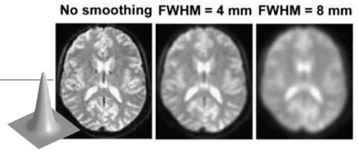
Pipeline of spatial normalization of PET



Spatial Normalization



Spatial Smoothing



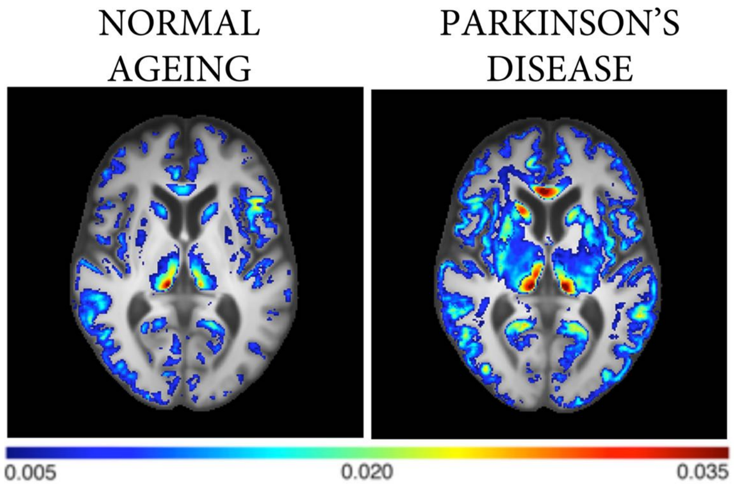
- The smoothing of images before statistical analysis is done for three main reasons:

1. Smoothing makes the data more normally distributed according to the central limit theorem
2. It compensates for the imperfections of spatial normalization by accounting for small interindividual anatomical differences that remain
3. Smoothing increases the sensitivity of the analysis to effects that are about the size of the smoothing kernel

Proportional scaling for PET

- In the case of PET, the amount of signal in the scan is dictated by the amount of radioactivity that has reached the head.
- PET counts may depend on:
  - Injected amounts of tracers
  - Received amounts of tracers
- Global nuisance effects can be accounted for either by proportional scaling, or ANCOVA

Performing statistical analysis



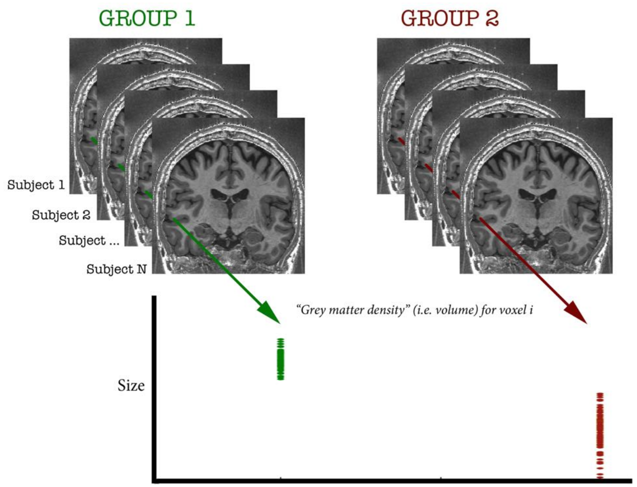
Classical statistics

- Parametric
  - one sample t-test
  - two sample t-test
  - paired t-test
  - Analysis of Variance (ANOVA)
  - Analysis of Covariance (ANCoVA)
  - correlation
  - linear regression
  - multiple regression

General Linear Model: a flexible framework for parametric analyses

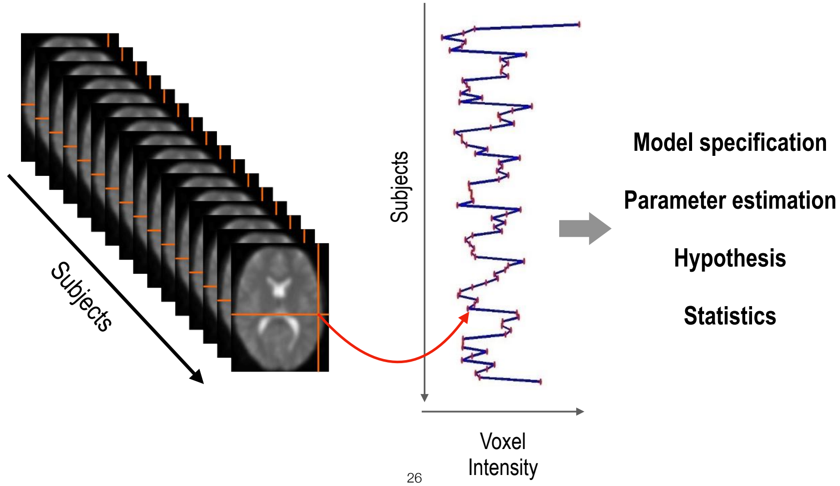
- Multivariate
- Non-parametric

A very simple experiment

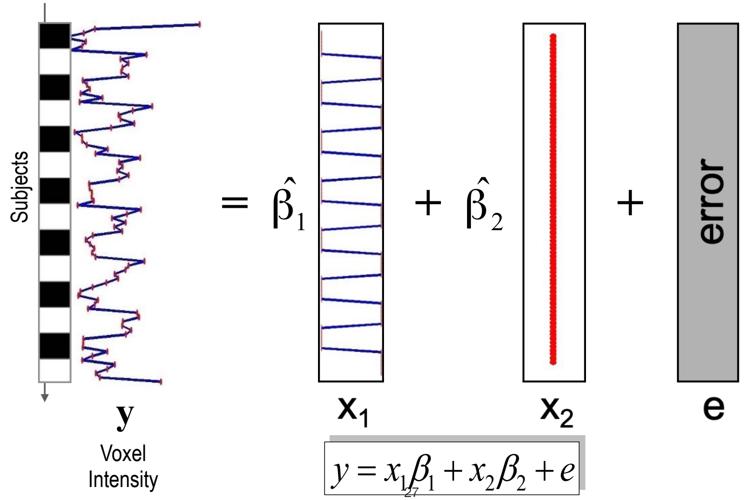


Question: Is there a change in the voxel intensity between groups?

Voxel-wise analysis



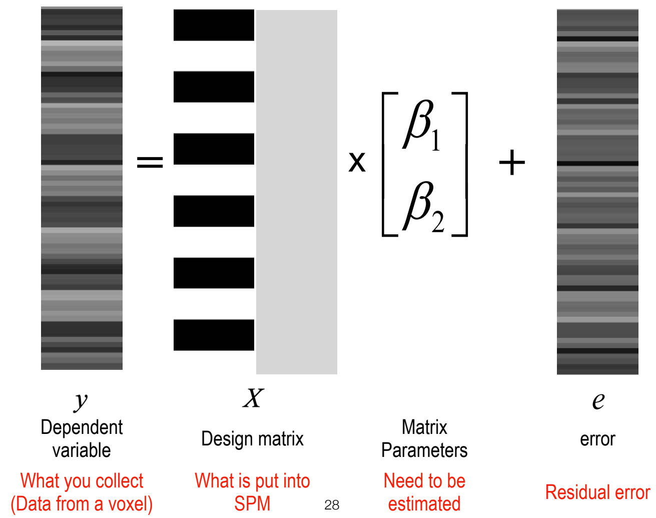
General Linear Model



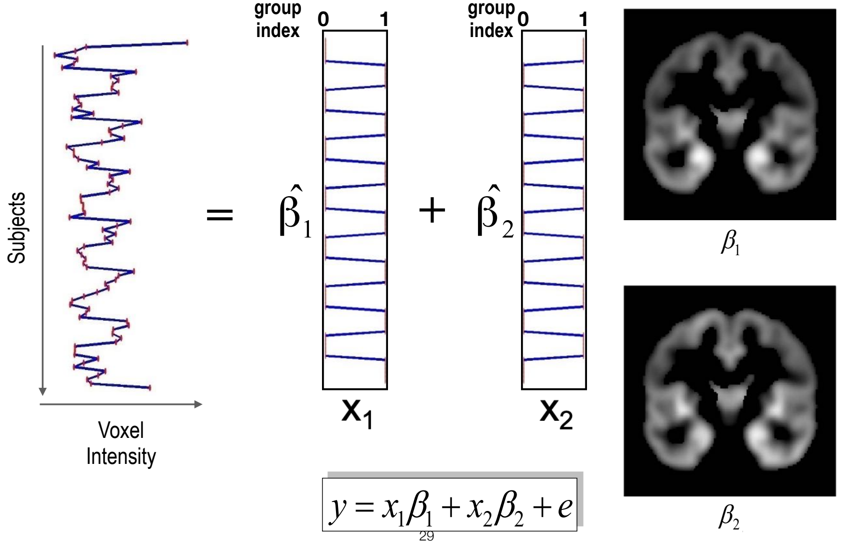
$$y = x_1\beta_1 + x_2\beta_2 + e$$

Parameter estimation

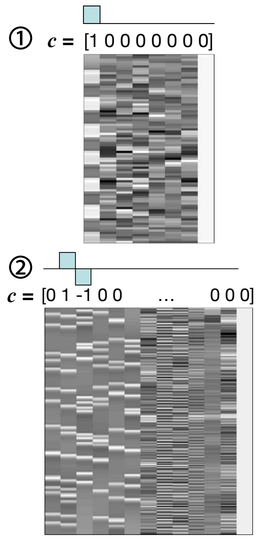
= Finding the "best" parameter values



One model to fit group difference



Contrast



- A contrast selects a specific effect of interest
  - A contrast $\boldsymbol{c}$ is a vector of length $\boldsymbol{p}$
  - $c \times \beta$ is a linear combination of regression coefficients β
- Null hypothesis : H_0: $c^T\beta=0$

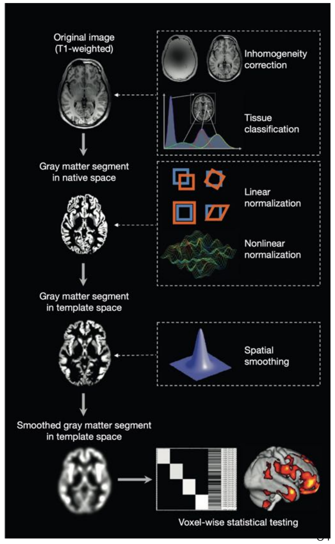
① $c = [1\ 0\ 0\ 0\ \ldots]^T$

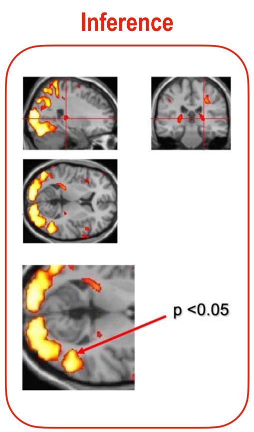
$$c^T\beta = \mathbf{1}\times\beta_1 + \mathbf{0}\times\beta_2 + \mathbf{0}\times\beta_3 + \mathbf{0}\times\beta_4 + \cdots$$
$$= \boldsymbol{\beta_1}$$

② $c = [0\ 1\ -1\ 0\ \ldots]^T$

$$c^T\beta = \mathbf{0}\times\beta_1 + \mathbf{1}\times\beta_2 + \mathbf{-1}\times\beta_3 + \mathbf{0}\times\beta_4 + \cdots$$
$$= \boldsymbol{\beta_2 - \beta_3}$$

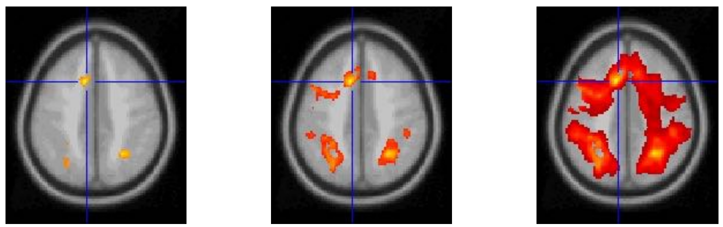
Statistical Parametric Mapping of PET





Assessing Statistic Images

High Threshold | **Med Threshold** | **Low Threshold**



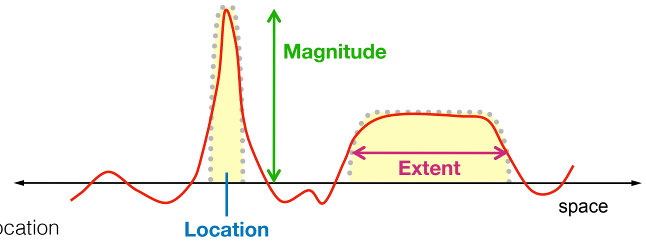
Good Specificity

Poor power
(risk of false negatives)

Poor Specificity
(risk of false positives)

Good power

Ideal Inference



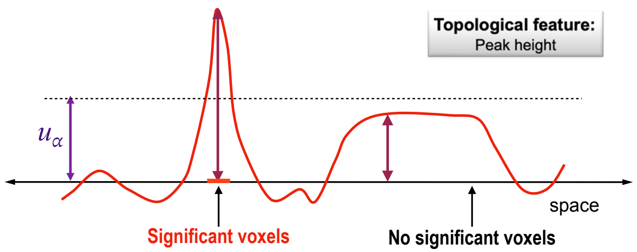
- Location
  - Estimates and confidence interval (CI)'s on specific location
- Magnitude
  - CI's on % change
- Spatial extent
  - Estimates and CI's on activation volume
  - Robust to choice of cluster definition

But this requires an explicit spatial model
We only have a univariate linear model at each voxel

Real-life Inference

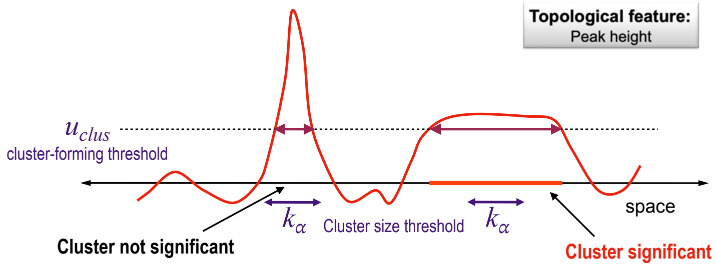
- Signal location
  - Local maximum - no inference
- Signal magnitude
  - Local maximum intensity - P-values (& CI's)
- Spatial extent
  - Cluster volume - P-value, no CI's
  - sensitive to blob-defining-threshold

Voxel-level Inference



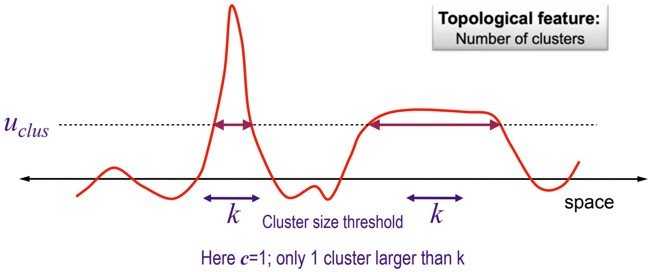
- Retain voxels above α-level threshold u_α
- Gives best spatial specificity
  - The null hypothesis at a single voxel can be rejected

Cluster-level Inference



- Two step-process
  - Define clusters by arbitrary threshold u_{clus}
  - Retain clusters larger than α-level threshold k_α
- Typically better sensitivity, Worse spatial specificity
  - The null hypothesis of entire cluster is rejected
  - Only means that one or more of voxels in cluster active

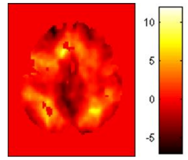
Set-level Inference

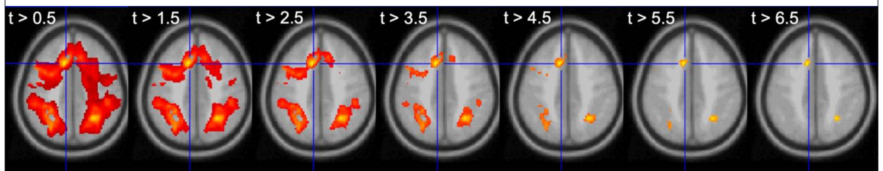


- Count number of blobs c
  - Minimum blob size k
- Worst spatial specificity
  - Only can reject global null hypothesis

Multiple Comparisons Problem

- Which of 100,000 voxels are significant?
  - α=0.05 ⇨ 5,000 false positive voxels
- Which of 100 cluster significant?
  - α=0.05 ⇨ 5 false positive clusters





Confusion matrix

Predicted values \ Actual values	Positive	Negative
Positive	True Positive	False Positive Type I error α
Negative	False Negative Type II error β	True Negative

MCP Solutions: Measuring False Positives

- Familywise Error Rate (FWER)
  - Familywise Error
    - Existence of one or more false positives, given the totsal number of statistical tests
  - FWER is probability of familywise error
  - Based on Random Field Theory
- False Discovery Rate (FDR)
  - FDR = E(V/R)
  - R voxels declared active, V falsely so
    - Realized false discovery rate: V/R

Summary

- Introduced VBM
- Spatial preprocessing of neuroimaging data
  - Preprocessing (coregister, normalization, smoothing)
  - Brain template (atlas)
  - Intensity (Count) normalization
- Statistics
- Inference

Thank you for your attention