Resting state fMRI and ICA

- Introduction to resting state
- Independent Component Analysis
- Single-subject ICA
- Multi-subject ICA
- Dual regression
Energy consumption in the brain

- Brain < 2% body weight but consumes ~20% of total energy
- estimated 60-80% of this energy used to support communication between cells
- task-evoked activity accounts for ~1%

Why study the brain at rest?

- Localisation versus connectivity

- Understand the inherent functional organisation of the brain

- Clinical/ cognitive biomarker

- Pragmatic benefits: can be done in any population, with relatively little setup and expertise required

Principles of resting state analysis

• Many different methods available for analysis

• All have one assumption in common:
  
  • i.e. definition of functional connectivity is based on a statistical dependency between timeseries

• Differences between methods lie in the way these similarities are estimated and/or represented

If two brain regions show similarities in their BOLD timeseries, they are functionally connected
Types of connectivity

- **Functional connectivity**
  - Statistical dependency

- **Dynamic connectivity**
  - Changes in functional connectivity over time

- **Effective connectivity**
  - Directional influence

- **Anatomical (structural) connectivity**
  - Presence of a white matter tract
Overview of resting state methods

Voxel-based methods

Node-based methods
Overview of resting state methods

**Voxel-based methods**
- Seed-based correlation analysis
  - SCA
- Independent component analysis
  - ICA

**Node-based methods**
- Network modelling analysis
  - FSLnets
- Graph theory analysis
  - Such as degree, hub, path length
Overview of resting state methods

**Voxel-based methods**

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Resting state methods

**ICA**
- Multivariate voxel-based approach
- Finds interesting structure in the data
- Exploratory “model-free” method
- Spatial approach

**Network modelling**
- Node-based approach (first need to parcellate the brain into functional regions)
- Map connections between specific brain regions (connectomics)
- Temporal approach
Model-based (GLM) analysis

- model each measured time-series as a linear combination of signal and noise
- If the design matrix does not capture every signal, we typically get wrong inferences!
Data Analysis

Confirmatory

Problem → Data → Model → Analysis → Results

- “How well does my model fit to the data?”
- results depend on the model

Exploratory

Problem → Data → Analysis → Model → Results

- “Is there anything interesting in the data?”
- can give unexpected results
FMRI inferential path

Experiment

Interpretation of final results

Analysis

MR Physics

Physiology
Variability in FMRI

Interpretation of final results

Experiment

suboptimal event timing, inefficient design, etc.

Physiology

secondary activation, ill-defined baseline, resting-fluctuations etc.

Analysis

filtering & sampling artefacts, design misspecification, stats & thresholding issues etc.

MR Physics

MR noise, field inhomogeneity, MR artefacts etc.
Model-free?

There is no explicit time-series model of assumed ‘activity’
Model-free?

\[ Y^i = S^i A^i + E^i, \quad \text{where} \quad E^i_j \sim \mathcal{N}(0, \sigma^2_I) \]

There is an underlying mathematical (generative) model
Decomposition techniques

- try to ‘explain’ / represent the data
  - by calculating quantities that summarise the data
  - by extracting underlying ‘hidden’ features that are ‘interesting’
- differ in what is considered ‘interesting’
  - are localised in time and/or space (Clustering)
  - explain observed data variance (PCA, FDA, FA)
  - are maximally independent (ICA)
Melodic

multivariate linear decomposition:
Melodic

multivariate linear decomposition:
Melodic

multivariate linear decomposition:

FMRI data = \text{components} \times \text{spatial maps}
Melodic

multivariate linear decomposition:

Data is represented as a 2D matrix and decomposed into components.
Melodic

multivariate linear decomposition:

$Y = \beta X$

Data is represented as a 2D matrix and decomposed into components.
What are components?

- express observed data as linear combination of spatio-temporal processes
- techniques differ in the way data is represented by components
Spatial ICA for FMRI

- data is decomposed into a set of spatially independent maps and a set of time-courses

McKeown et al.
HBM 1998
Independence
PCA vs. ICA?

Simulated Data

(2 components, slightly different timecourses)
Simulated Data

(2 components, slightly different timecourses)
PCA vs. ICA?

Simulated Data
(2 components, slightly different timecourses)

PCA
- Timecourses orthogonal
- Spatial maps and timecourses “wrong”
PCA vs. ICA?

Simulated Data
(2 components, slightly different timecourses)

PCA
• Timecourses orthogonal
• Spatial maps and timecourses “wrong”

ICA
• Timecourses non-co-linear
• Spatial maps and timecourses “right”
PCA vs. ICA

- PCA finds projections of maximum amount of variance in Gaussian data (uses 2nd order statistics only)

Gaussian data
PCA vs. ICA

• PCA finds projections of maximum amount of variance in Gaussian data (uses 2nd order statistics only)

• Independent Component Analysis (ICA) finds projections of maximal independence in non-Gaussian data (using higher-order statistics)
Correlation vs. independence

- de-correlated signals can still be dependent
- higher-order statistics (beyond mean and variance) can reveal these dependencies

Stone et al. 2002
Non-Gaussianity
Non-Gaussianity

non-Gaussian

mixing

Gaussian
ICA estimation

- Random mixing results in more Gaussian-shaped PDFs (Central Limit Theorem)

- Conversely:
  
  if mixing matrix produces less Gaussian-shaped PDFs this is unlikely to be a random result

  ➡️ measure non-Gaussianity

- can use neg-entropy as a measure of non-Gaussianity
ICA estimation

- need to find an unmixing matrix such that the dependency between estimated sources is minimised
- need (i) a contrast (objective/cost) function to drive the unmixing which measures statistical independence and (ii) an optimisation technique:
  - kurtosis or cumulants & gradient descent (Jade)
  - maximum entropy & gradient descent (Infomax)
  - neg-entropy & fixed point iteration (FastICA)
Overfitting & thresholding
The ‘overfitting’ problem

fitting a noise-free model to noisy observations:
- no control over signal vs. noise (non-interpretable results)
- statistical significance testing not possible

GLM analysis  standard ICA (unconstrained)
Probabilistic ICA model

statistical “latent variables” model: we observe linear mixtures of hidden sources in the presence of Gaussian noise

\[ Y = X \beta + \text{noise} \]

Issues:
- Model Order Selection: how many components?
- Inference: how to threshold ICs?
Model Order Selection

‘How many components’?

under-fitting: the amount of explained data variance is insufficient to obtain good estimates of the signals

optimal fitting: the amount of explained data variance is sufficient to obtain good estimates of the signals while preventing further splits into spurious components

over-fitting: the inclusion of too many components leads to fragmentation of signal across multiple component maps, reducing the ability to identify the signals of interest
Model Order Selection

- observed Eigenspectrum of the data covariance matrix
- Laplace approximation of the posterior probability of the model order
- theoretical Eigenspectrum from Gaussian noise
Model Order Selection

- **green** observed Eigenspectrum of the data covariance matrix
- **red dashed** Laplace approximation of the posterior probability of the model order
- **blue dashed** theoretical Eigenspectrum from Gaussian noise

The graph shows the relationship between the number of components and the model order selection. The optimal fit is indicated by the point where the observed Eigenspectrum aligns with the Laplace approximation. The region marked as under-fitting is where the model is too simple to capture the data's complexity, while over-fitting occurs when the model is too complex, leading to unnecessary detail.
Model Order Selection

- observed Eigenspectrum of the data covariance matrix
- Laplace approximation of the posterior probability of the model order
- theoretical Eigenspectrum from Gaussian noise
Thresholding

raw Z transformed IC map (1 - 99 percentile)

Mixture Model probability map

thresholded IC map alternative hypothesis test at $p > 0.5$
Thresholding

- classical null-hypothesis testing is invalid
- data is assumed to be a linear combination of signals and noise
- the distribution of the estimated spatial maps is a mixture distribution!
Alternative Hypothesis Test

- use Gaussian/Gamma mixture model fitted to the histogram of intensity values (using EM)
What about overlap?
What about overlap?

Sources  ⇢  Sources + noise  ⇢  ICA solution  ⇢  after thresholding

\[ \rho = 0.5 \quad \rho < 0.1 \quad \rho = 0 \quad \rho \approx 0.5 \]
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Artefact detection

- FMRI data contain a variety of source processes
- Artifactual sources typically have unknown spatial and temporal extent and cannot easily be modelled accurately
- Exploratory techniques do not require a priori knowledge of time-courses and spatial maps
FSLeyes Melodic Mode
motion
cardiac
susceptibility motion
multiband
signal
effects of scan parameters
manual classification

https://doi.org/10.1016/j.neuroimage.2016.12.036
ICA-based denoising
ICA-based denoising

\[ Y = X\beta + e \]
ICA-based denoising

\[ Y = X\beta + e \]

cleaned fMRI data
semi-automatic classification

component -> classifier -> signal or noise label
semi-automatic classification

• FIX (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIX)
  • Classifier with many features
  • Requires manually labelled training data
  • 99% accuracy on high-quality data
semi-automatic classification

• FIX (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIX)
  • Classifier with many features
  • Requires manually labelled training data
  • 99% accuracy on high-quality data

• ICA-AROMA (github.com/rhr-pruim/ICA-AROMA)
  • Simple classifier with only 4 features
  • No training data required
  • Mainly designed for motion artefacts
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Different ICA models

**Single-Session ICA**

- each ICA component comprises:
  - spatial map & timecourse

**Multi-Session or Multi-Subject ICA: Concatenation approach**

- each ICA component comprises:
  - spatial map & timecourse
  - (that can be split up into subject-specific chunks)

**Multi-Session or Multi-Subject ICA: Tensor-ICA approach**

- each ICA component comprises:
  - spatial map, session-long-timecourse & subject-strength plot
Different ICA models

**Single-Session ICA**

Each ICA component comprises:
- spatial map & timecourse

**Multi-Session or Multi-Subject ICA:**

*Concatenation approach*

Good when:
- Each subject has **different** timeseries
  - E.g. resting-state FMRI

**Multi-Session or Multi-Subject ICA:**

*Tensor-ICA approach*

Good when:
- Each subject has **same** timeseries
  - E.g. activation FMRI
Concatenated ICA

- Concatenate all subjects’ data temporally
- Then run ICA
- More appropriate than tensor ICA (for RSNs)
Concatenated ICA

- Data sets must be registered to a common space (anatomical alignment)

- Memory optimisation trick (called MIGP) means that time courses are not interpretable

\[
\text{Subject 1} \times \text{voxels} = \text{group ICA maps} \\
_\vdots \\
\text{Subject 2} \times \text{voxels} = \text{group ICA maps}
\]
Resting state multi-subject ICA

- Why not just run ICA on each subject separately?
  - Correspondence problem (eg RSNs across subjects)
  - Different splittings sometimes caused by small changes in the data (naughty ICA!)
- Instead - start with a “group-average” ICA
  - But then need to relate group maps back to the individual subjects
Resting state networks
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Resting state multi-subject ICA

Group ICA map

Example subject maps derived from dual regression
Two steps that both involve multiple regression:

1. Extract subject timeseries
2. Extract subject maps
1. Regress group maps into each subject’s 4D data to find subject-specific timecourses

2. Regress these timecourses back into the 4D data to find subject-specific spatial maps
Dual Regression

Group ICA map

Example subject maps derived from dual regression
Running dual_regression

FSL command line tool, combining:

- DR to create subject-wise estimates (stage 1 + stage 2)
- Group comparison using randomise (stage 3)
Group comparison

- Collect maps and perform voxel-wise test (e.g. randomisation test on GLM)
- Can now do voxelwise testing across subjects, separately for each original group ICA map
- Can choose to look at strength-and-shape differences

#subjects × #EVs = collected components

voxels = group difference

R L R L
Group analysis on maps

- can use the Glm tool (Glm_gui on mac) to create GLM design and contrast matrices
Dual regression outputs

- `dr_stage1_subject[#SUB].txt` - the timeseries outputs of stage 1 of the dual-regression.
Dual regression outputs

- \texttt{dr\_stage1\_subject[#SUB].txt} - the timeseries outputs of stage 1 of the dual-regression.

- \texttt{dr\_stage2\_subject[#SUB].nii.gz} - the spatial maps outputs of stage 2 of the dual-regression.
Dual regression outputs

- `dr_stage1_subject[#SUB].txt` - the timeseries outputs of stage 1 of the dual-regression.

- `dr_stage2_subject[#SUB].nii.gz` - the spatial maps outputs of stage 2 of the dual-regression.

- `dr_stage2_ic[#ICA].nii.gz` - the re-organised parameter estimate images
Dual regression outputs

- `dr_stage1_subject[#SUB].txt` - the timeseries outputs of stage 1 of the dual-regression.

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- `dr_stage2_ic[#ICA].nii.gz` - the re-organised parameter estimate images

- `dr_stage3_ic[#ICA]_tstat[#CON].nii.gz` - the output from randomise
Dual regression outputs

- `dr_stage1_subject[#SUB].txt` - the timeseries outputs of stage 1 of the dual-regression.
- `dr_stage2_subject[#SUB].nii.gz` - the spatial maps outputs of stage 2 of the dual-regression.
- `dr_stage2_ic[#ICA].nii.gz` - the re-organised parameter estimate images
- `dr_stage3_ic[#ICA]_tstat[#CON].nii.gz` - the output from `randomise`

(corrected for multiple comparisons across voxels but not across #components!!)
Group template maps

- Generate from the data using ICA
- Use all data to get unbiased templates

Template RSNs

https://www.fmrib.ox.ac.uk/datasets/royalsoc8/
Group template maps

- Generate from the data using ICA
- use all data to get unbiased templates
- use independent control group
- will model signals and artefacts

template RSNs
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template RSNs

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Available from:
- Oxford University Press
- Amazon