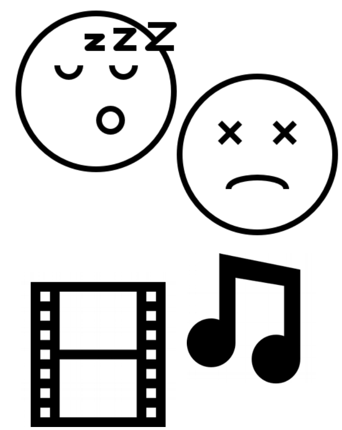
Biomarkers extracted from fMRI data for cognition and neuropathologies

Matthieu Gilson and Gorka Zamora-López

Center for Brain and Cognition, Univ Pompeu Fabra, Barcelona (Spain)

Human Brain Project – SP4 / WP4.4

?



Vicente Pallarés, Andrea Insabato, Ana Sanjuán
Gorka Zamora-López, Nikos Kouvaris,
Katharina Glomb, Gustavo Deco







CBC
CENTER FOR BRAIN & COGNITION

upf. Universitat Pompeu Fabra Barcelona

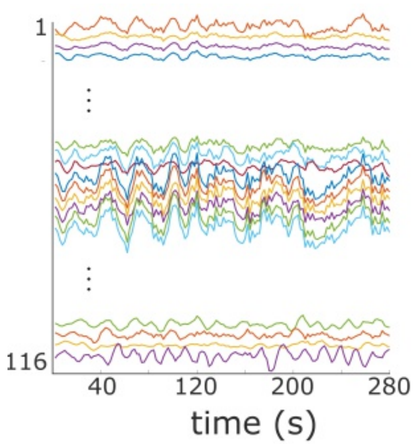
European Commission

Human Brain Project

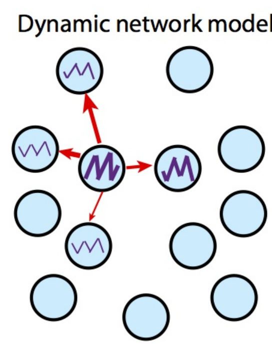
MARIE CURIE ACTIONS

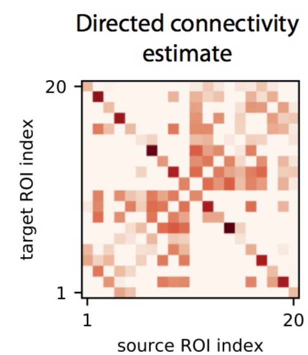
Biomarker for cognition: Task-evoked fMRI

Brain activity recorded via scanner

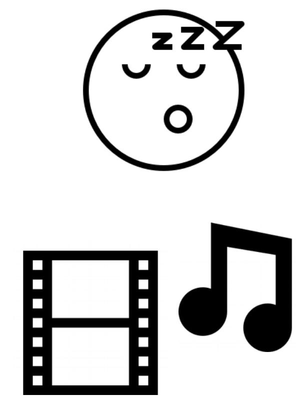


Connectivity measure



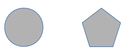


Cognitive state (e.g. task)



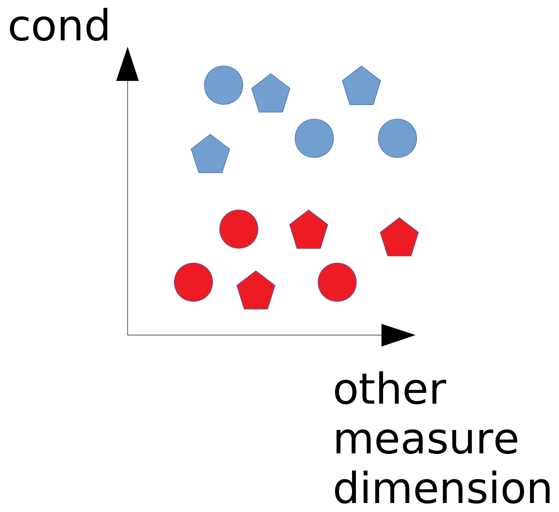
Classification of cognitive states

Condition 1
Condition 2



subjects

desired situation

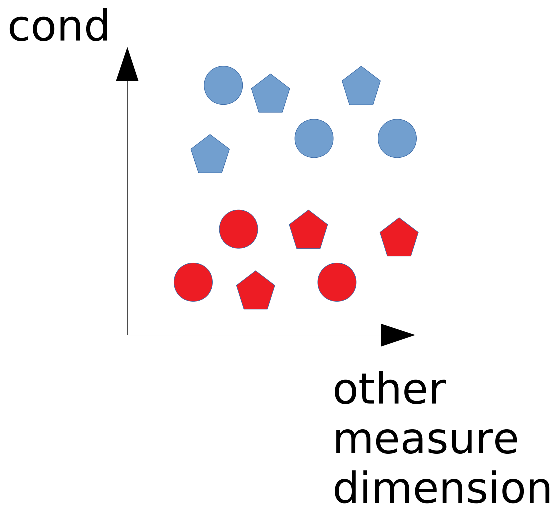


Classification of cognitive states

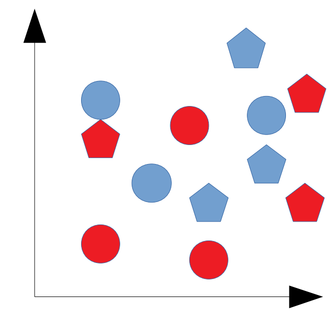
Condition 1
Condition 2

subjects

desired situation

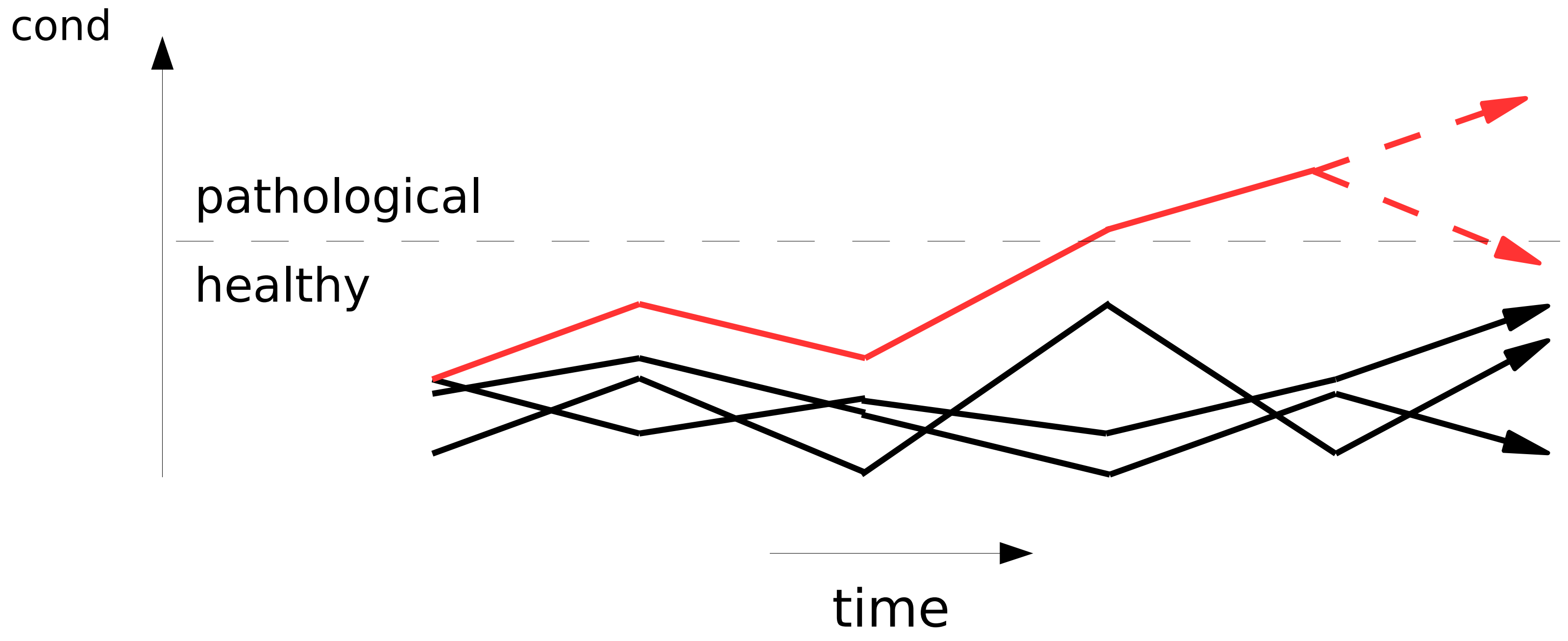


useless measure
(or data...)



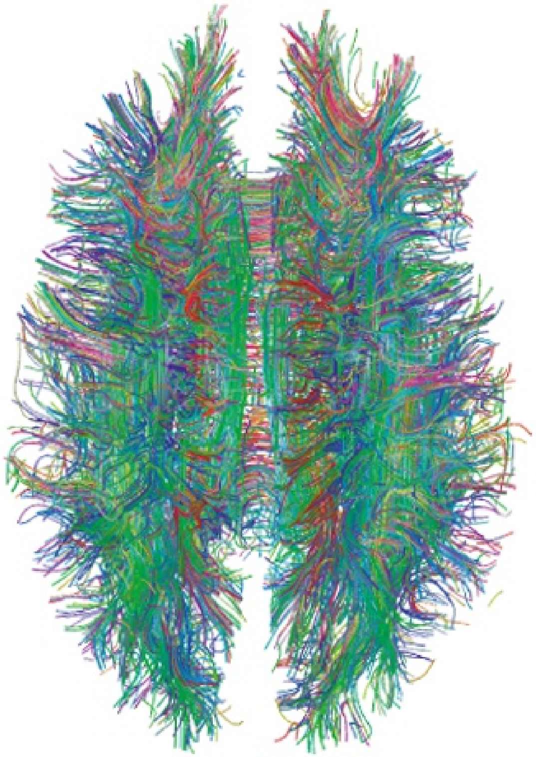
Neuroimaging-based clinical diagnostic

- Goal: classify patient's condition over time, for example during medication trial (getting better/worse?)

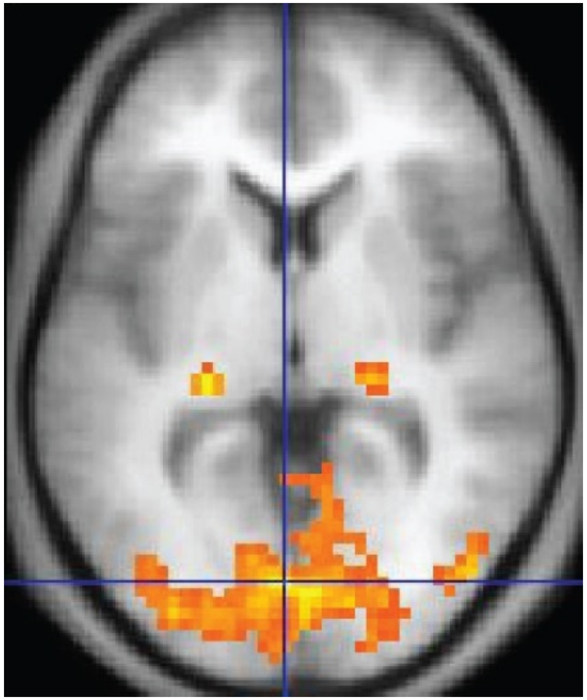


Neuroimaging-based clinical diagnostic

- Goal: classify patient's condition over time, for example during medication trial (getting better/worse?)
- Structural data? Depends on disease (not for depression, schizophrenia, ...)

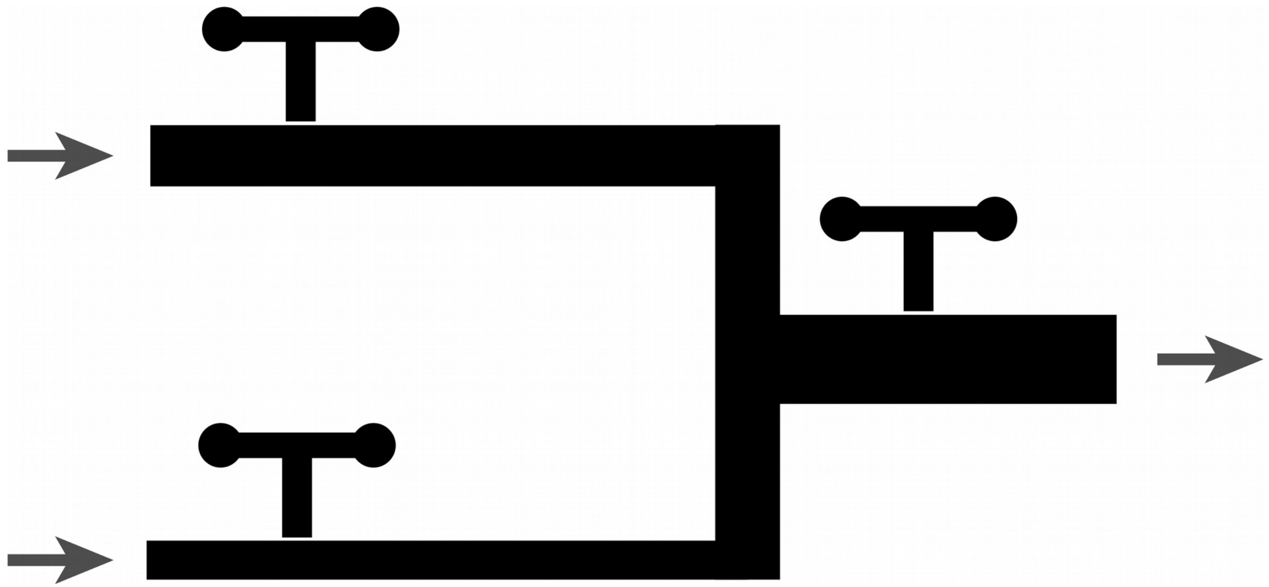


wikipedia



Limitations of SC as biomarker

- Anatomical SC = infrastructure; does not take into account synaptic receptors, neuromodulators, etc.
- Good to study strokes, Alzheimer disease, etc.
- Not suitable to explore task-specific brain communication
- Water supply network analogy: size of tubes ≠ how much each tap is open (which determines the flow)



Resting-state fMRI activity reflects pathologies

Curr Opin Neurol. 2008 Aug;21(4):424-30. doi: 10.1097/WCO.0b013e328306f2c5.

Resting-state functional connectivity in neuropsychiatric disorders.

Greicius M[1].

Author information

Abstract

PURPOSE OF REVIEW: This review considers recent advances in the application of resting-state functional magnetic resonance imaging to the study of neuropsychiatric disorders.

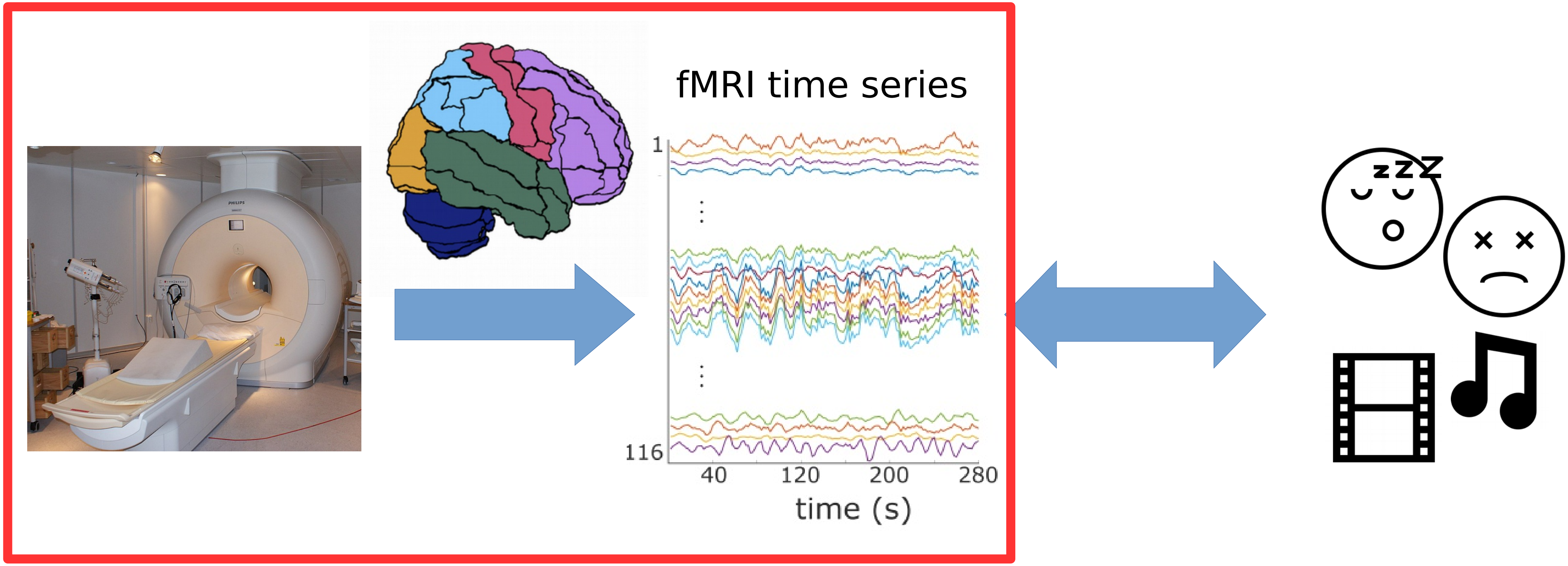
SUMMARY: Resting-state functional magnetic resonance imaging has made some strides in the clinical realm but significant advances are required before it can be used in a meaningful way at the single-patient level.

Outline

- Connectivity measures for fMRI data
- Identification of task/subject using EC-based classification
- Network theory

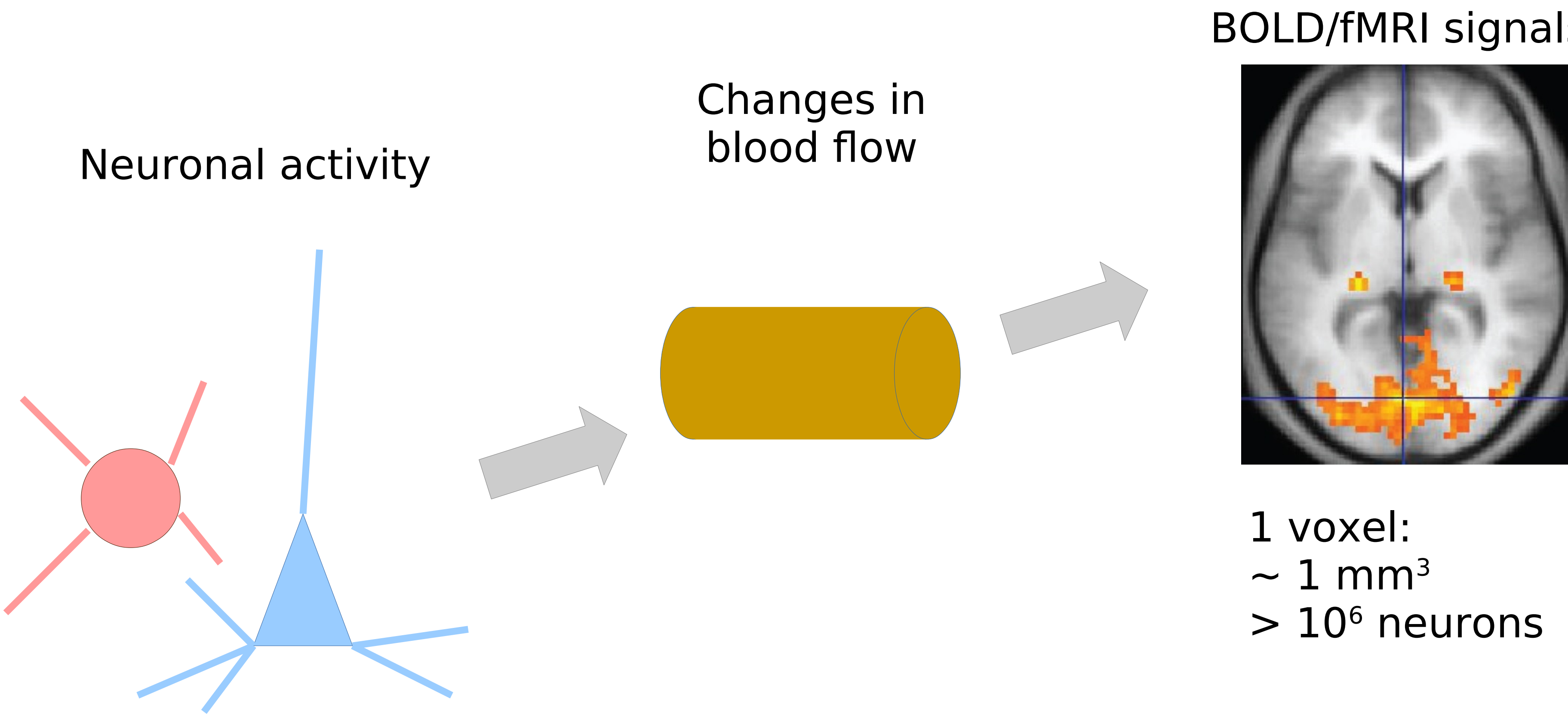
- Reference: Gilson et al. (bioRxiv) “MOU-EC: model-based whole-brain effective connectivity to extract biomarkers for brain dynamics from fMRI data and study distributed cognition”; http://doi.org/10.1101/531830
- Open-access preprints on http://matthieugilson.eu/publications.html
- Code: http://github.com/MatthieuGilson/pyMOU
- HBP collab: http://collab.humanbrainproject.eu/#/collab/48372/

Quantitative methods for fMRI analysis



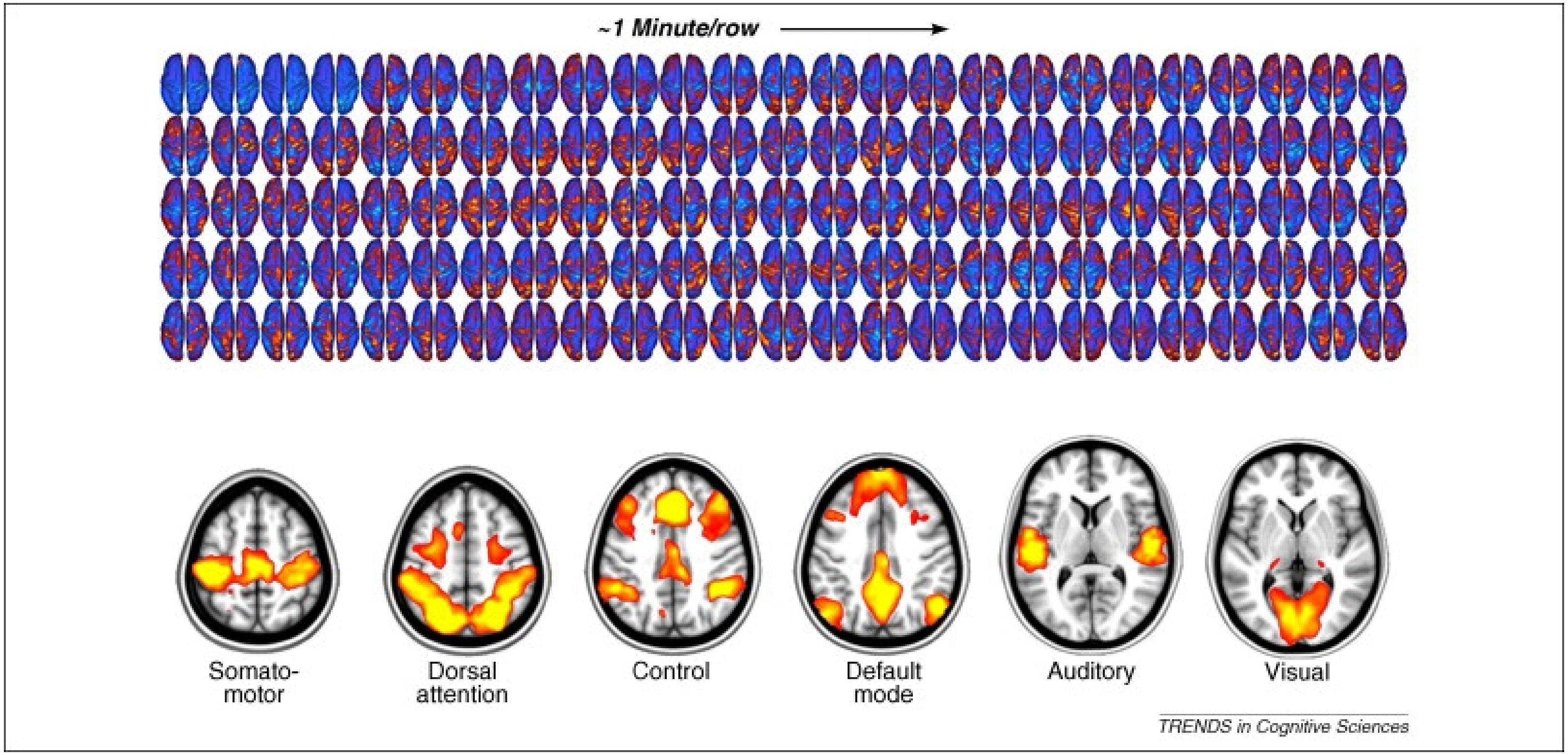
- Where is information in fMRI signals?
- What is their structure?

Blood-oxygen-level-dependent (BOLD) signals



- Logothetis et al. (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature
- Stephan et al. (2004) Biophysical models of fMRI response. Neuroimage
- Logothetis (2012) What We Can and What We Can’t Do with fMRI. Nat Neurosci

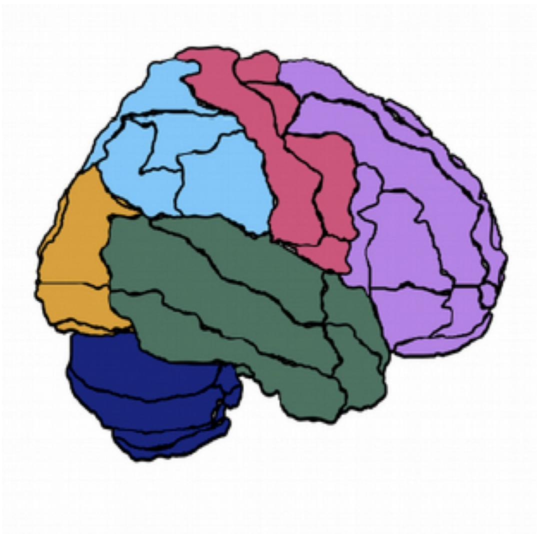
BOLD correlations: functional connectivity (FC)

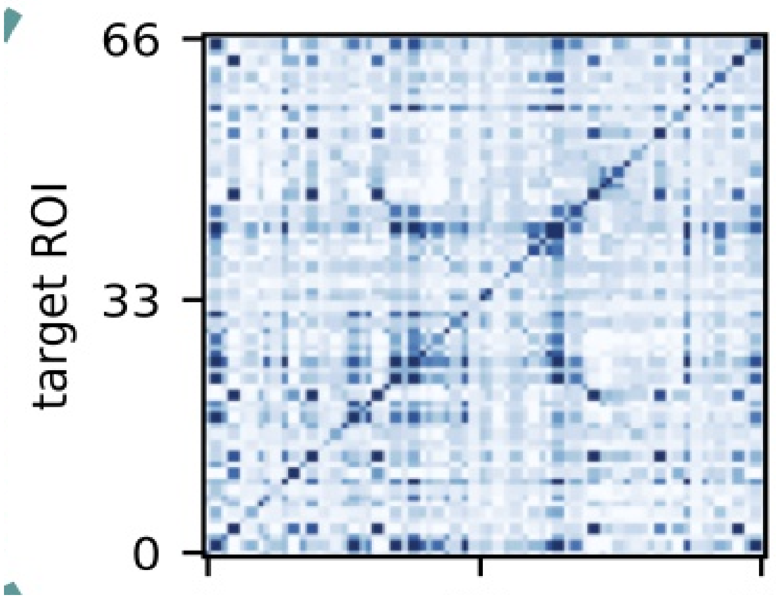


Raichle, Trend Cog Sci (2010);
Mantini et al., PNAS (2007)

- Even at rest, distant brain areas exhibit correlated BOLD activity
- PCA/ICA applied on BOLD signals (but also EEG and MEG) reveals resting-state networks

BOLD correlations: functional connectivity (FC)

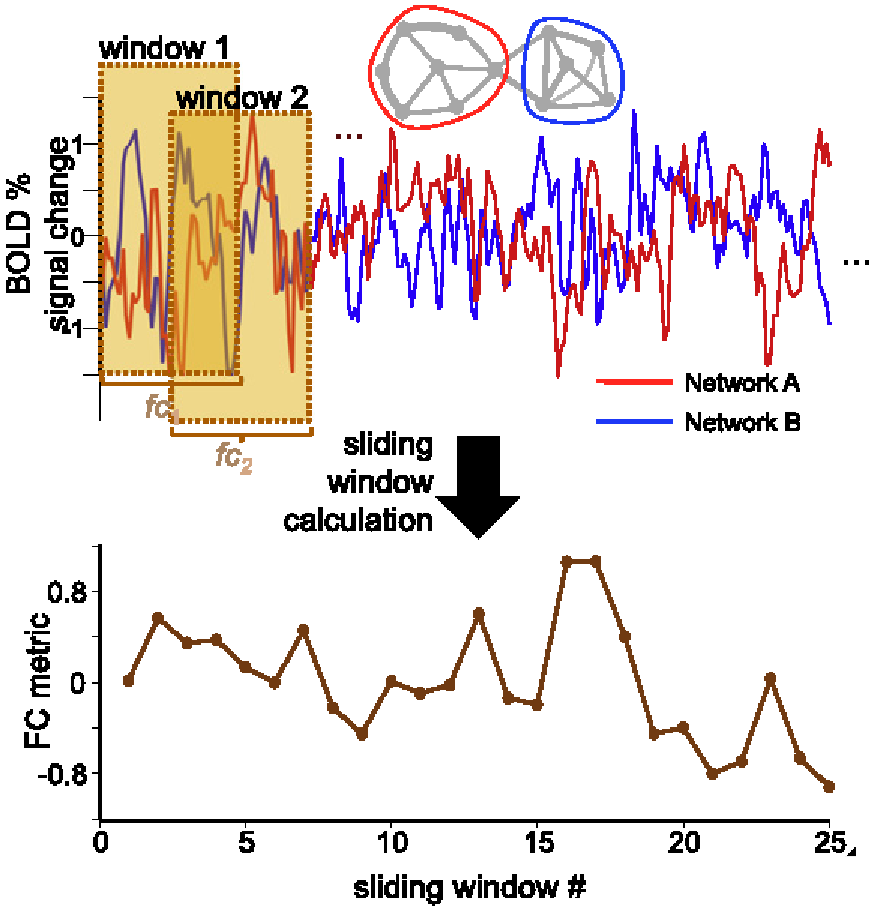




- Even at rest, distant brain areas exhibit correlated BOLD activity
- PCA/ICA applied on BOLD signals (but also EEG and MEG) reveals resting-state networks
- FC = superposition of RSN expression over time

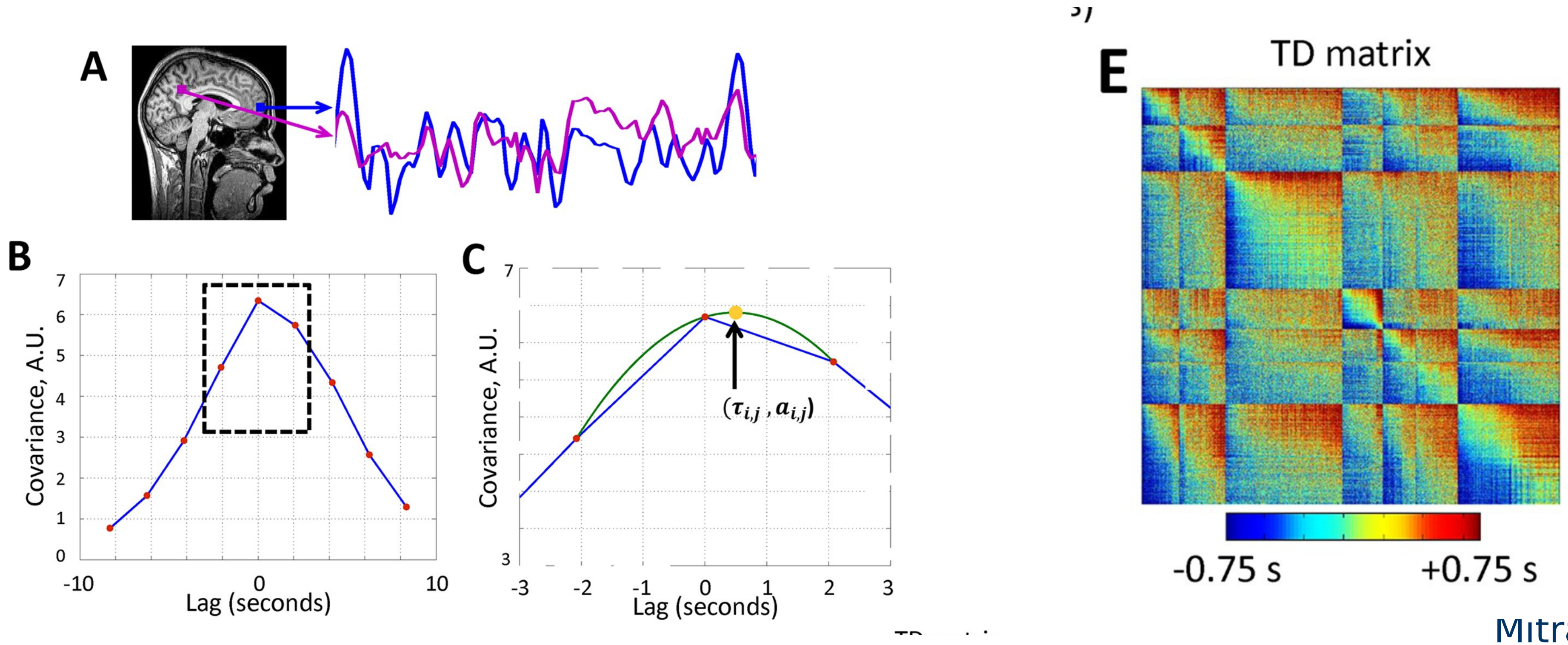
Dynamic functional connectivity

- Measure of calculated using sliding window (also using Hilbert transform)
- Study of transition between brain “activity states”
- Assumption of stationarity within sliding window (timescale of 1 minute)



Hutchison et al. 2013 Neuroimage

Temporal structure in BOLD signals



Mitra et al. 2015 eLife

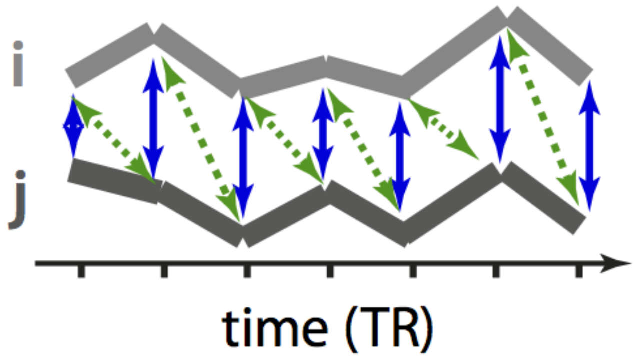
- Shorter time scale (BOLD resolution = 1 TR ~ 2 seconds)
- Lag structure (TD matrix) with early/late ROIs

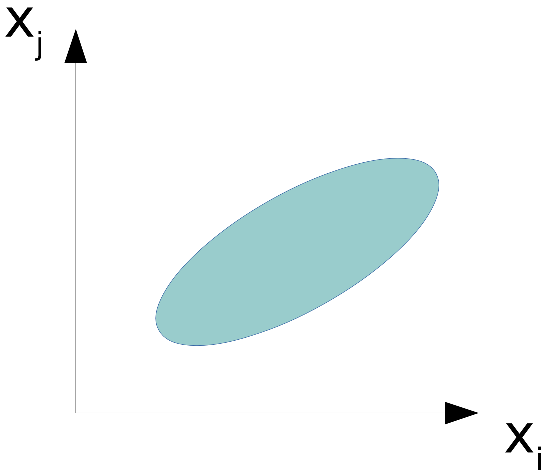
Typology of measures

	Without time	"Linear" in time domain	"Linear" in frequency domain	Others; non-linear
Nodal measure	Variance	Auto-covariance	Power spectrum	
Connectivity measures and estimates	Covariances, Pearson correlation	Cross-covariances	Cross-spectrum, coherence	Mutual information
	Partial correlation	Auto-regressive process	Partial coherence	Conditional mutual information

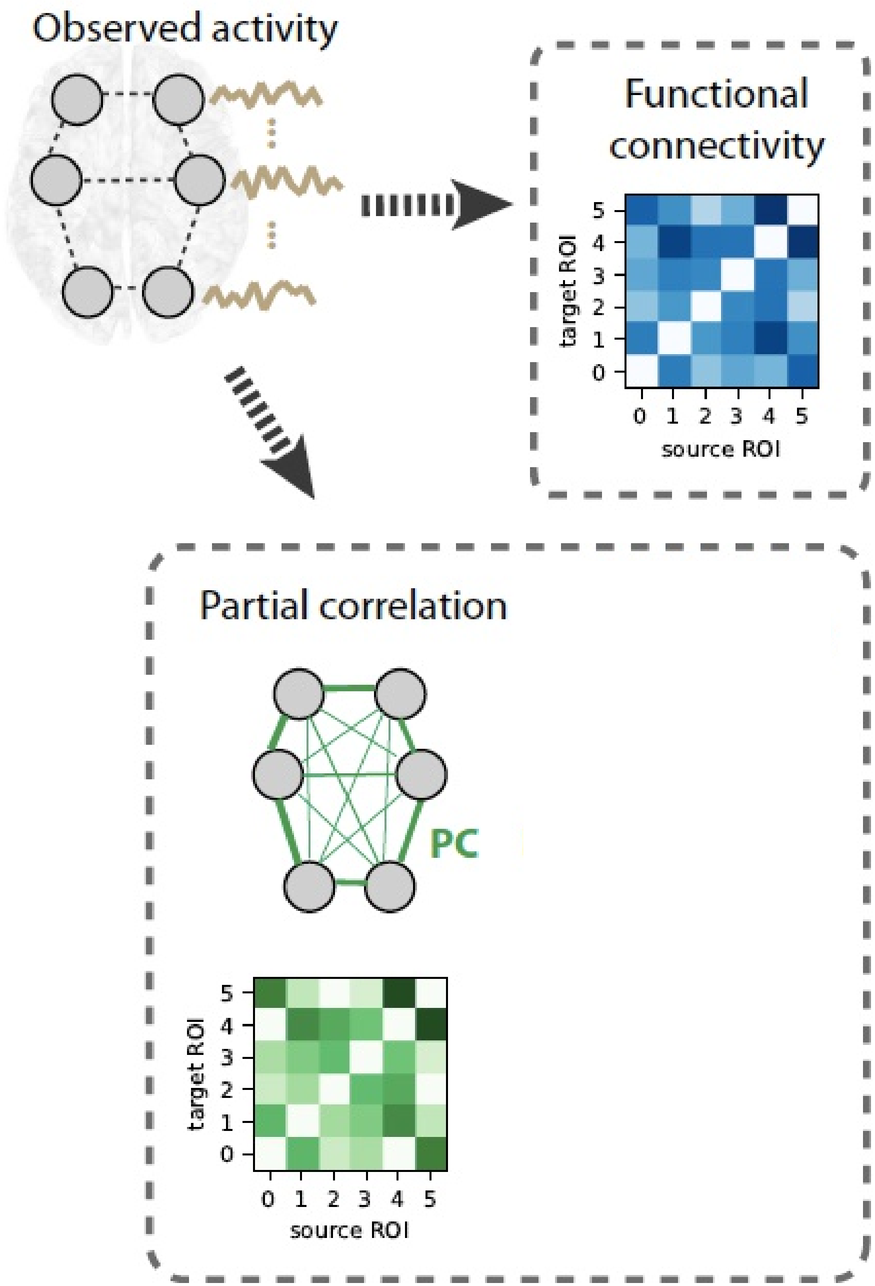
Traditional FC

- FC evaluated using Pearson correlation
- Underlying model: graphical model = Gaussian variables
- No time involved: time series as succession of independent samples
- Structure determined by 2nd-order statistics (covariances without time lag: blue arrows only)





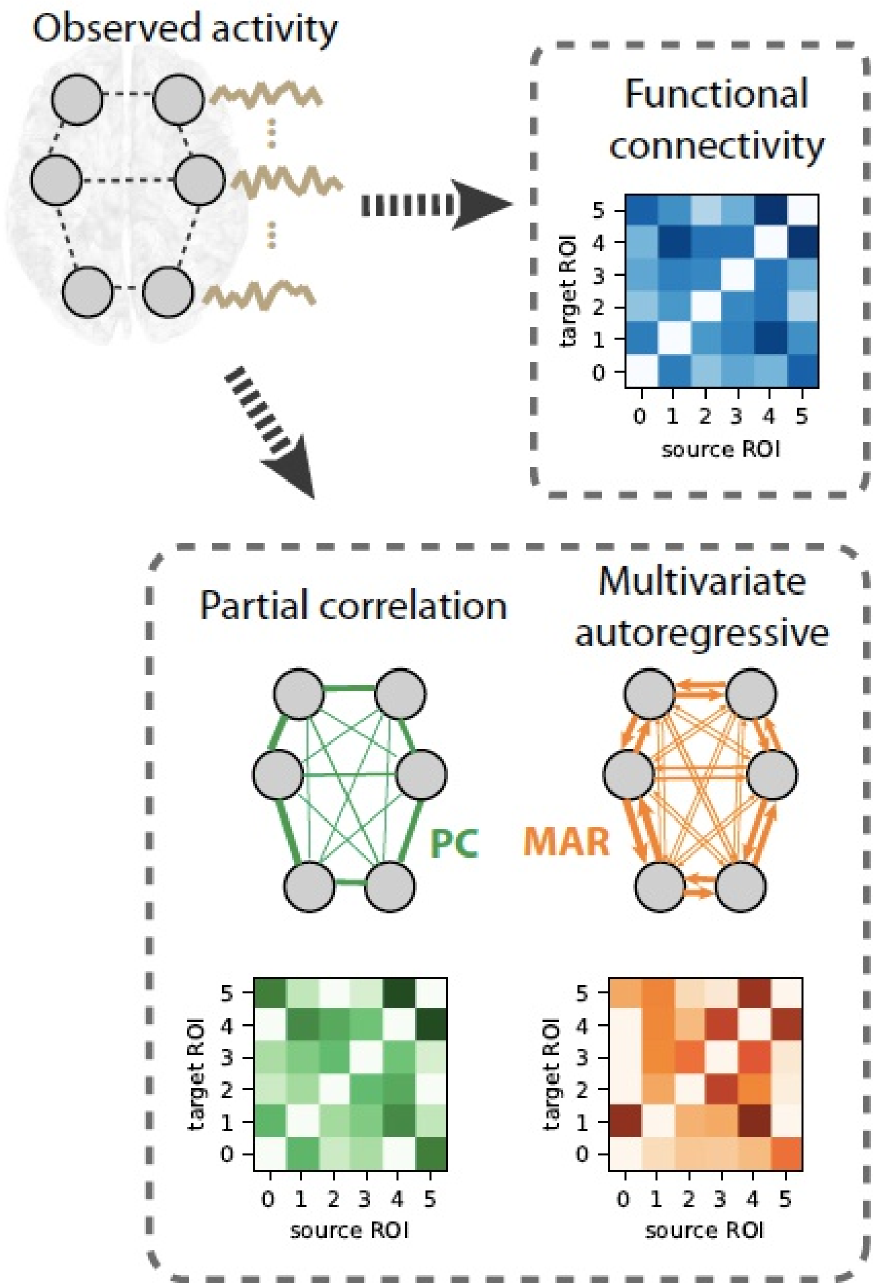
Observed activity versus model inversion



Observed correlations

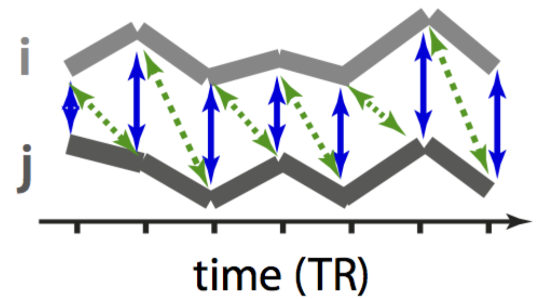
Interactions that explain observed correlations

Observed activity versus model inversion



Observed correlations

WITH TIME LAG FOR MAR



Interactions that explain observed correlations

Typology of measures

	Without time	"Linear" in time domain	"Linear" in frequency domain	Others; non-linear
Nodal measure	Variance	Auto-covariance	Power spectrum	
Connectivity measures and estimates	Covariances, Pearson correlation	Cross-covariances	Cross-spectrum, coherence	Mutual information
	Partial correlation	Auto-regressive process	Partial coherence	Conditional mutual information

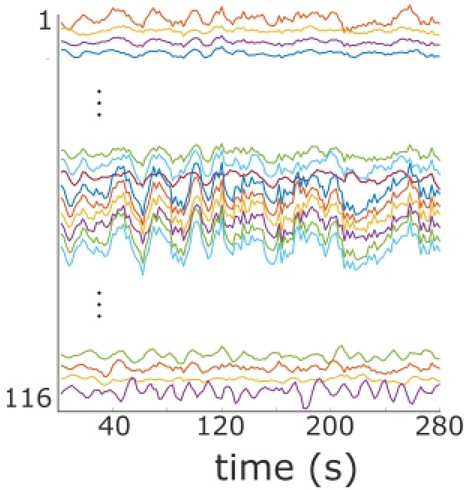
MODEL INVERSION

“Why a model?”

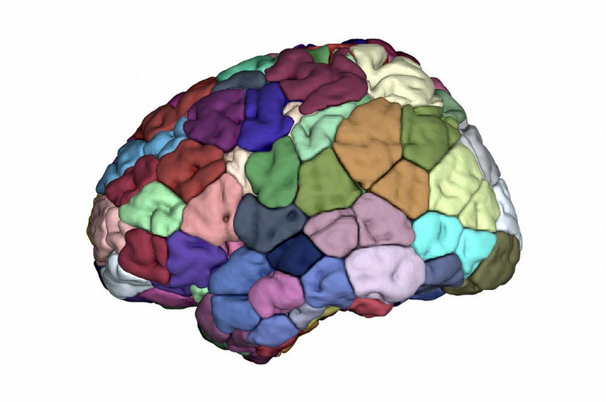
- Every connectivity measure implies a model
- Model as hypothesis
  - phenomenological model → characterize data structure
  - mechanistic model → assemble biophysical mechanisms
- Better know hypotheses implied by choice of model

Whole-brain modeling

fMRI/BOLD signals



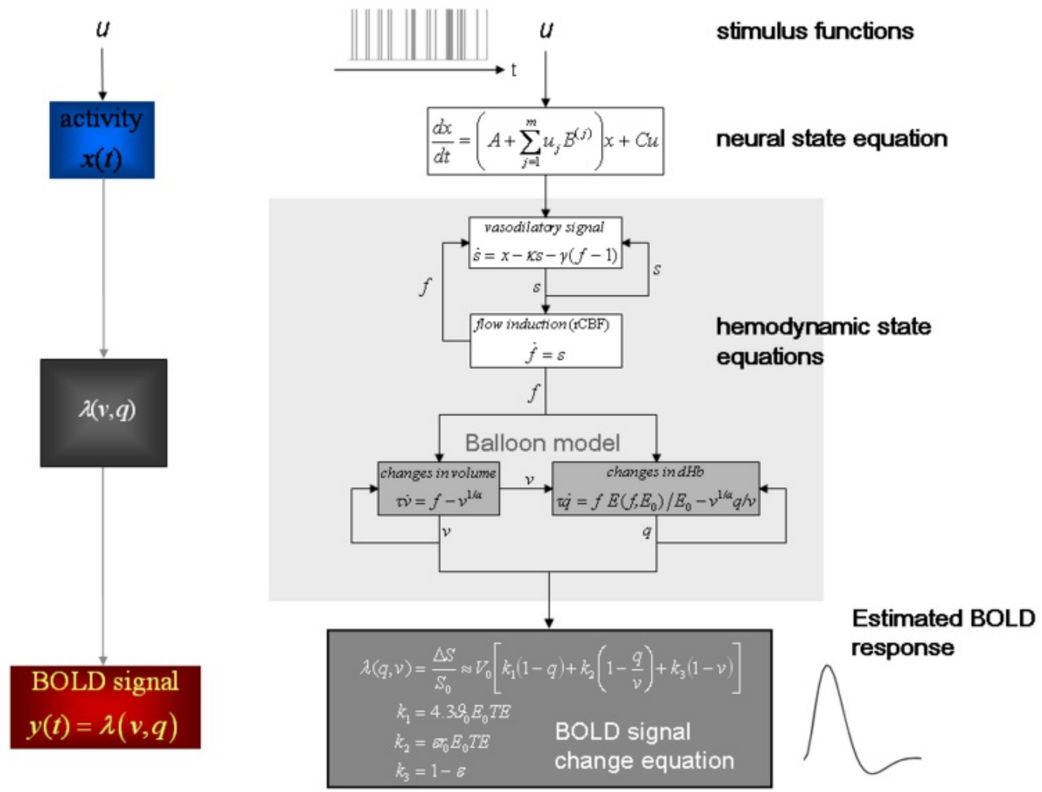
Whole-brain parcellation

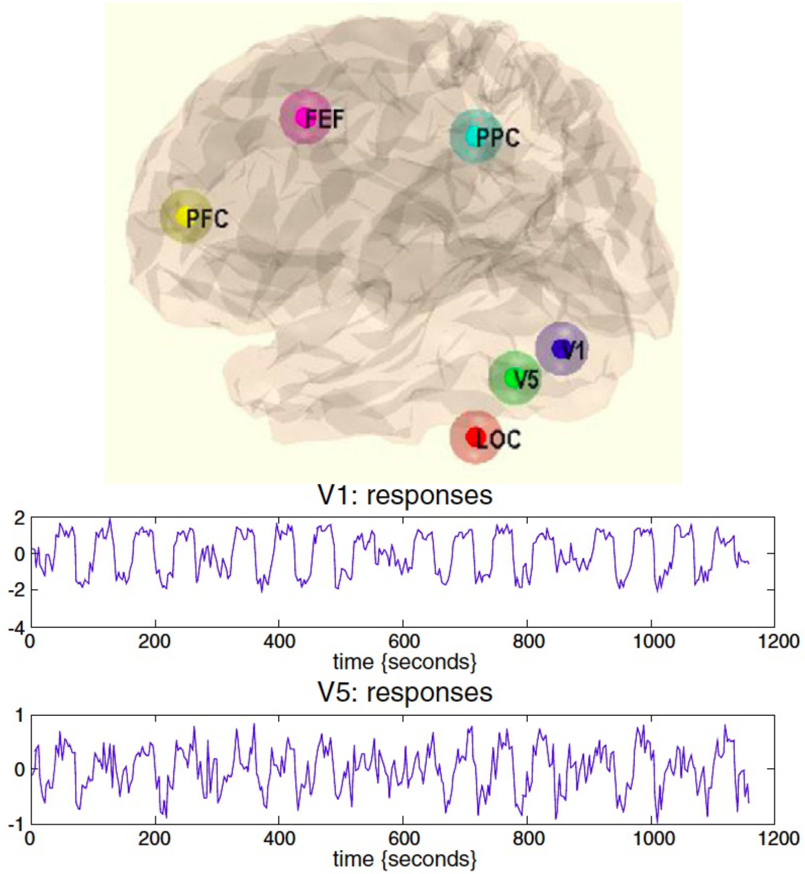


- Observable of BOLD signals
- Choice for regions of interest (ROIs) and parcellation

Dynamic causal model (DCM)

- Neural dynamics
- Hemodynamics
- Initially a-priori selected ROIs; now whole brain version





Friston et al. (2003) Dynamic Causal Modelling. Neuroimage

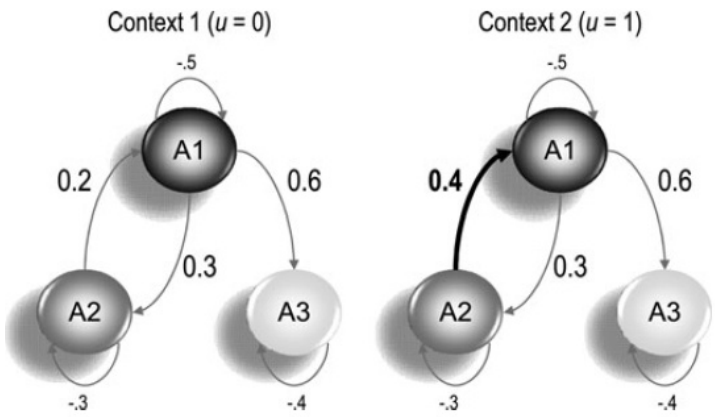
Stephan et al. (2004) Biophysical models of fMRI response. Neuroimage

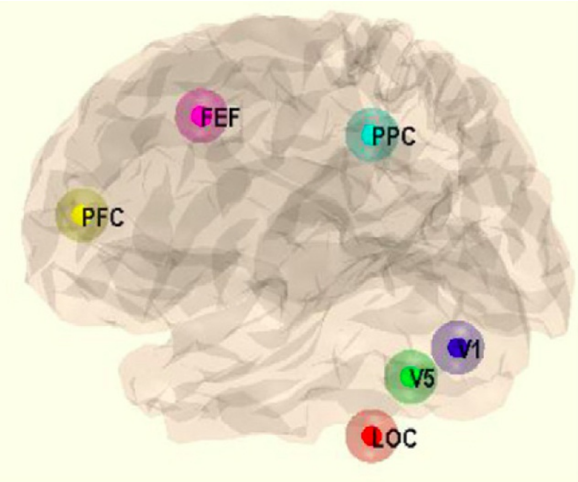
Friston (2011) Functional and Effective Connectivity: A Review. Brain Connect

Frässle et al. (2017) Regression DCM for fMRI. Neuroimage

Effective connectivity (EC) for DCM

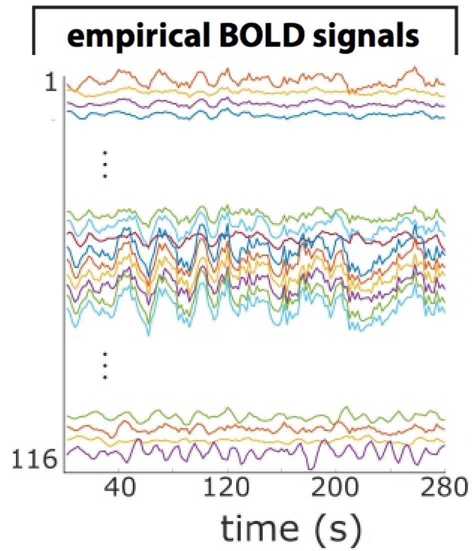
- Directed connectivity between brain regions in model
- Significantly strong connections?
- Changes in estimated weights across conditions?

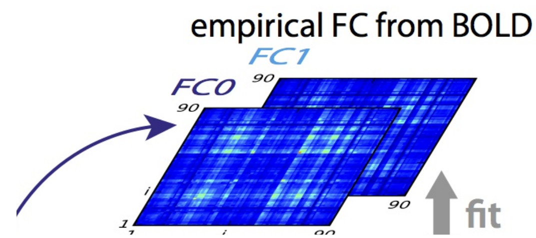


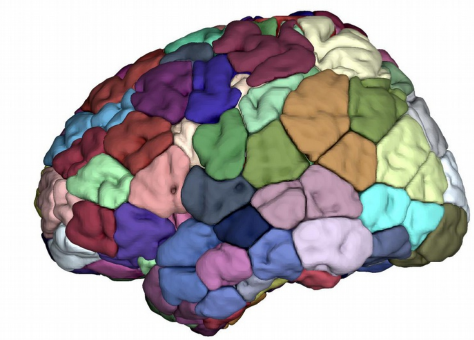


Friston et al. (2003) Dynamic Causal Modelling. Neuroimage
Stephan et al. (2004) Biophysical models of fMRI response. Neuroimage
Friston (2011) Functional and Effective Connectivity: A Review. Brain Connect
Frässle et al. (2017) Regression DCM for fMRI. Neuroimage

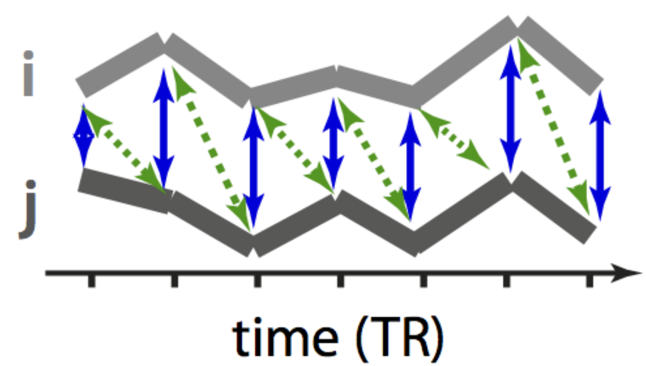
Our model: goal is to capture spatio-temporal structure of whole-brain BOLD







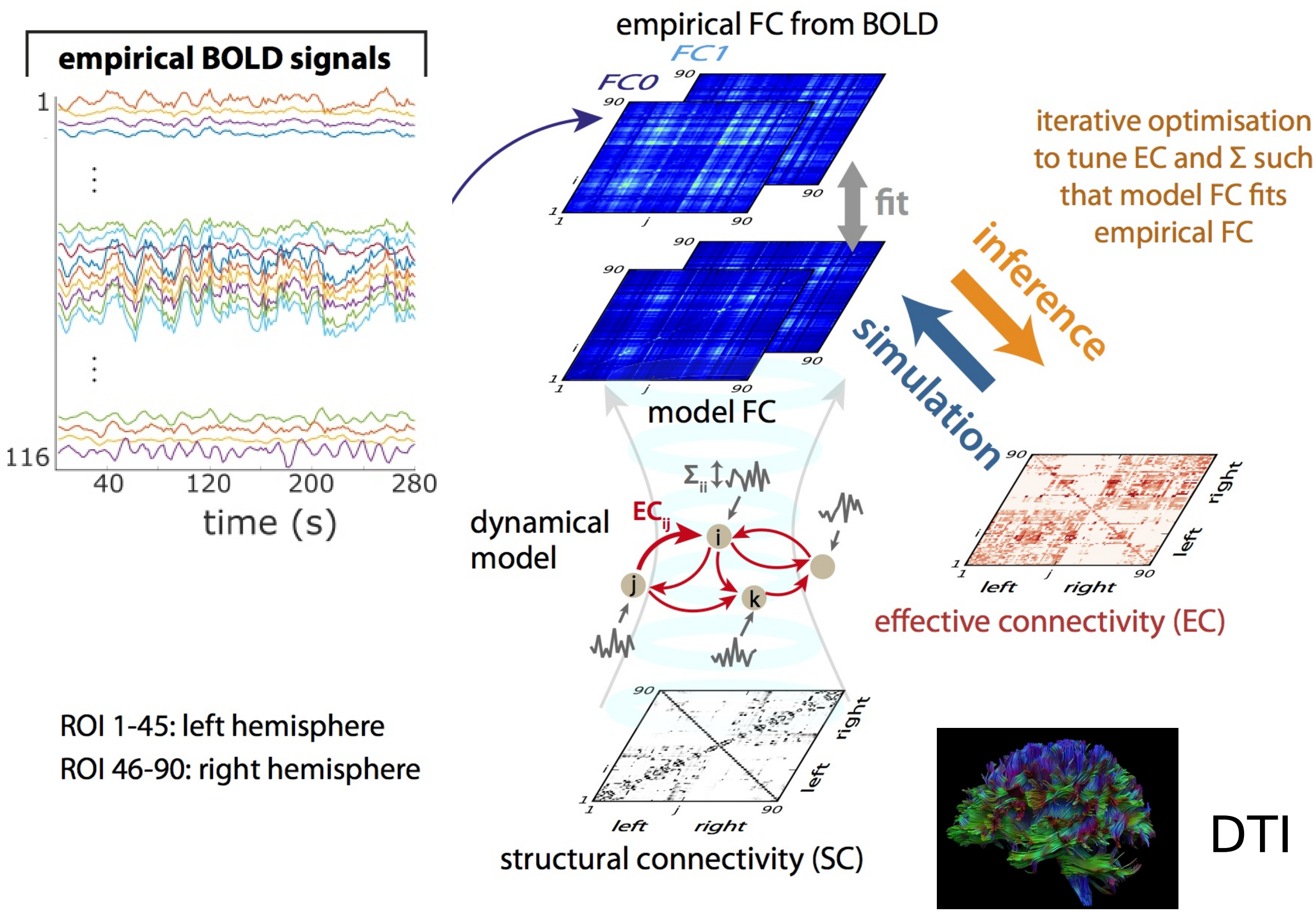
2 FC matrices:
- covariances without time shift
- covariances with time shift (1 TR)



ROI 1-45: left hemisphere
ROI 46-90: right hemisphere

Region of interest (ROI)

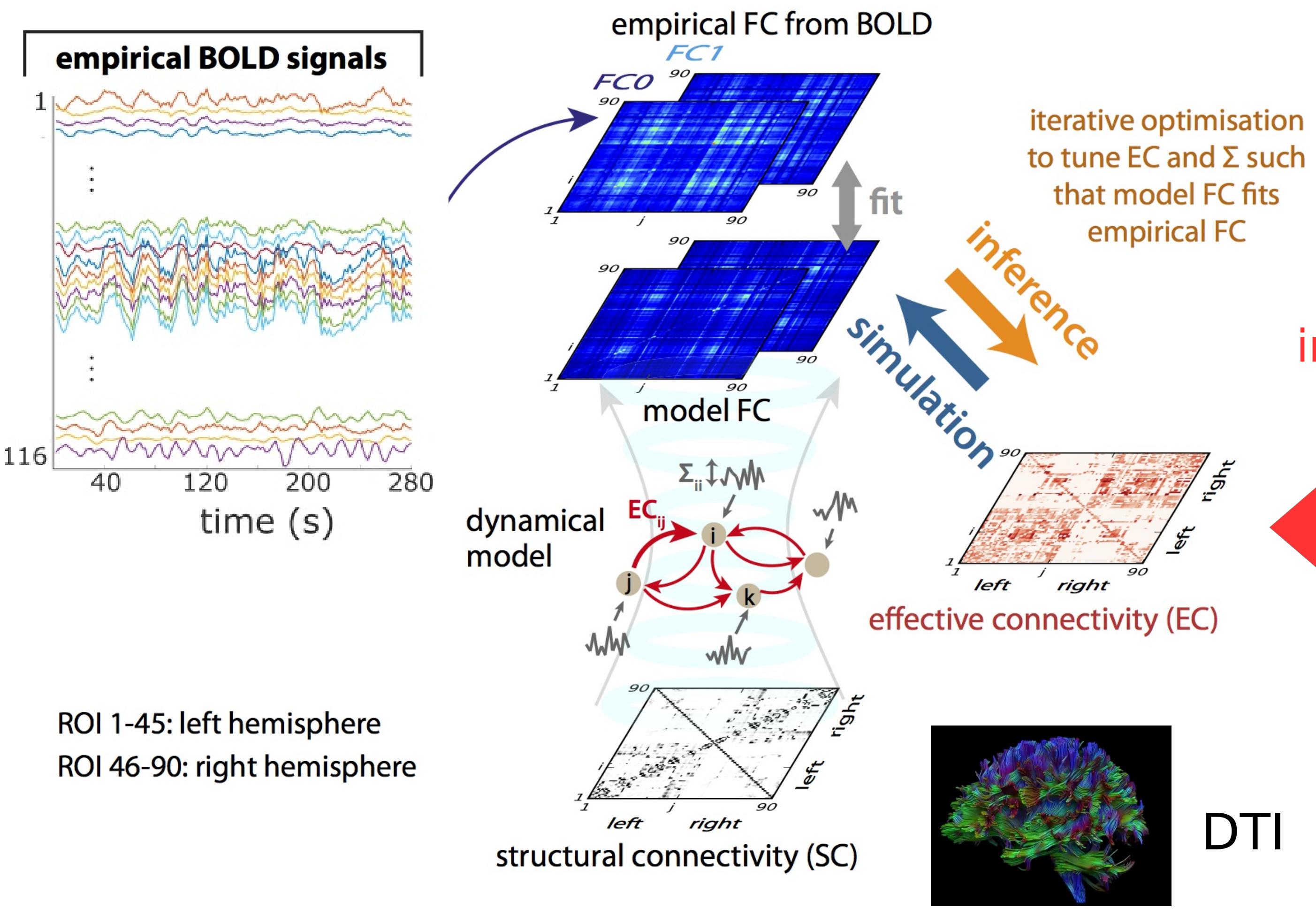
MOU-EC to capture brain "dynamical state"



2 ways to use model:

- Bottom-up → simulate and explore qualitatively behavior
- Top-down → "project" data on space of model parameters

MOU-EC to capture brain "dynamical state"



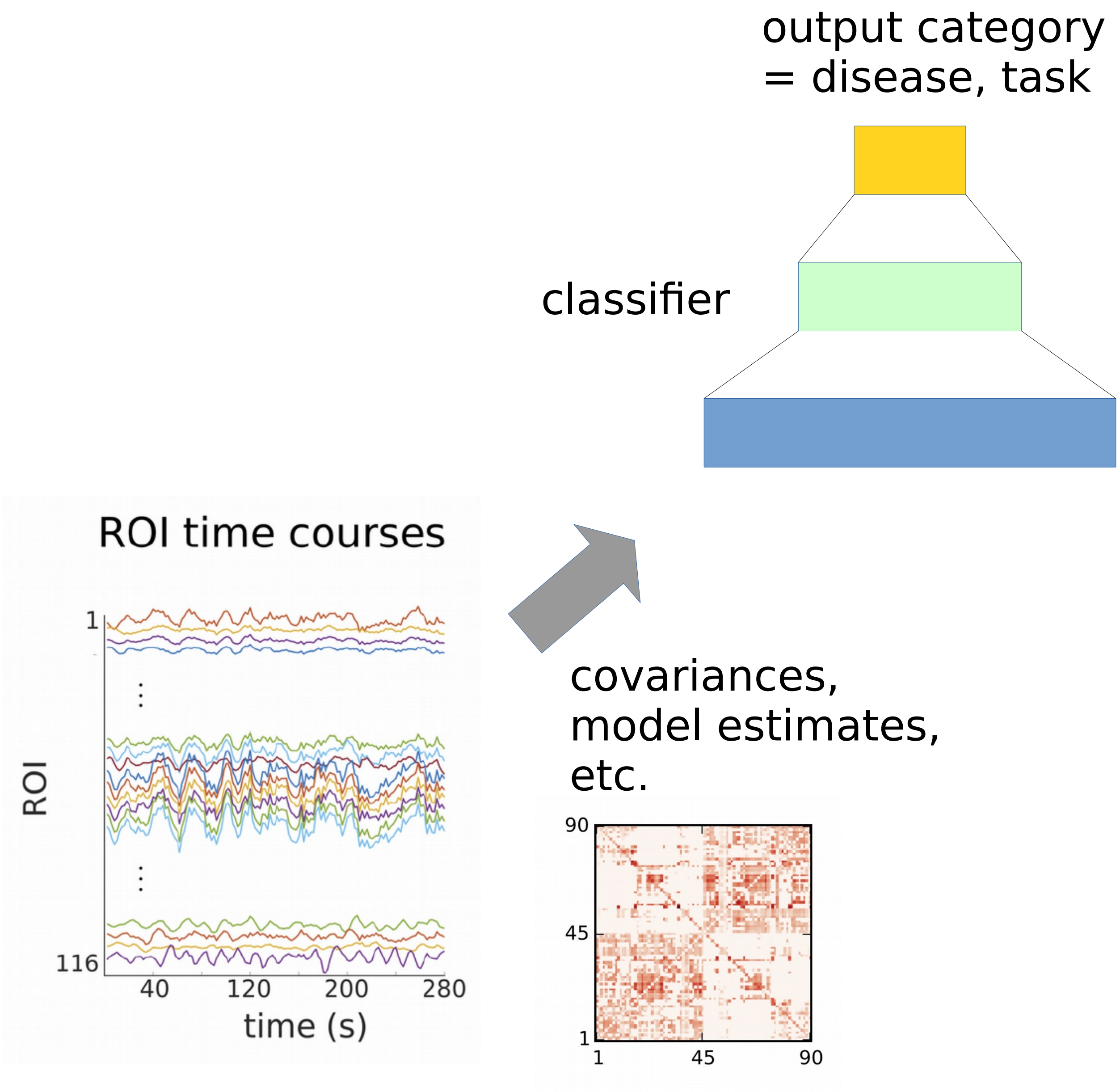
directed matrix of interactions between ROIs

DTI

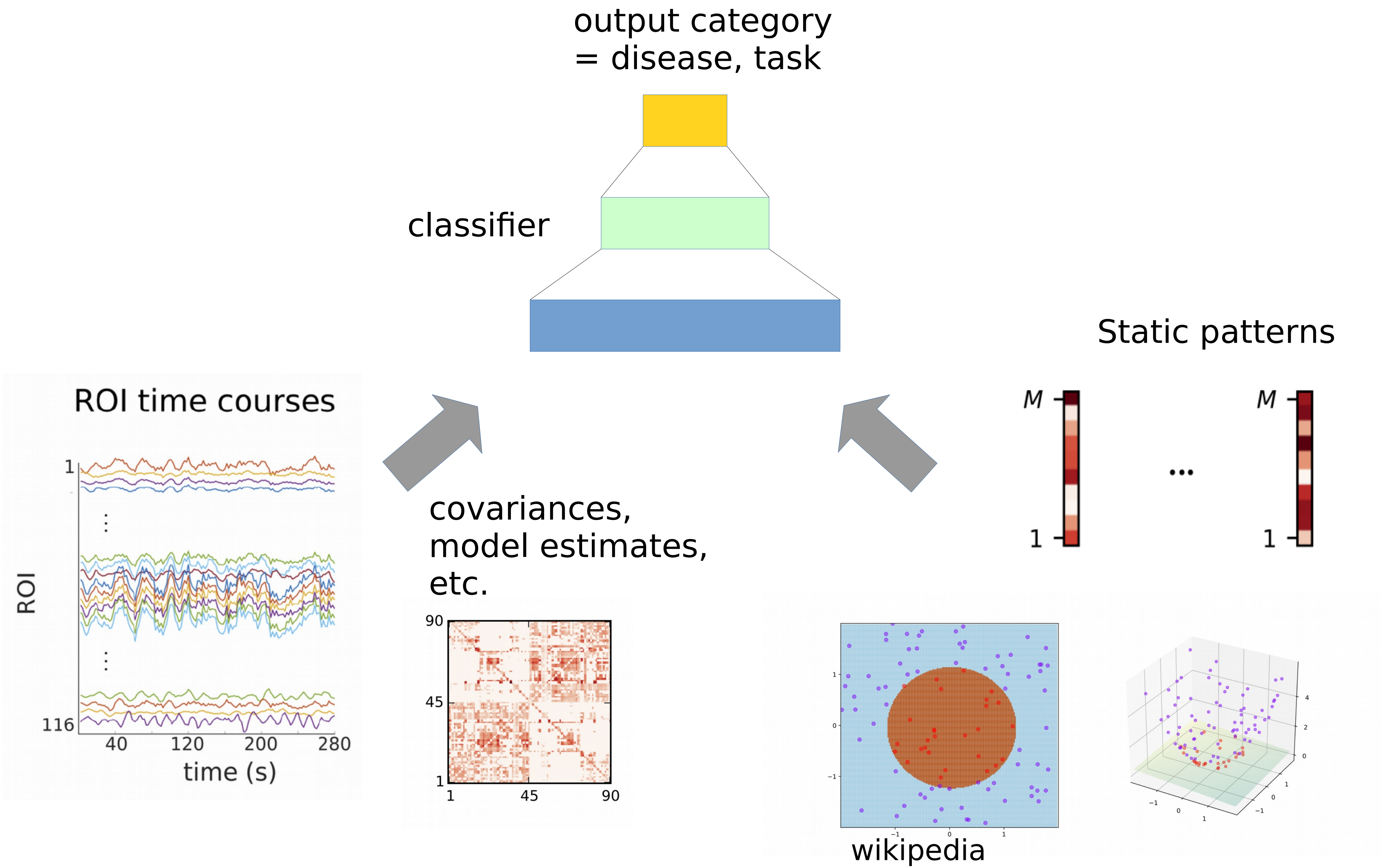
- Phenomenological dynamic model
- 70-100 ROIs → 1000-3000 EC weights

Gilson et al. PLoS Comput Biol 2016

Mode-based approach for classification

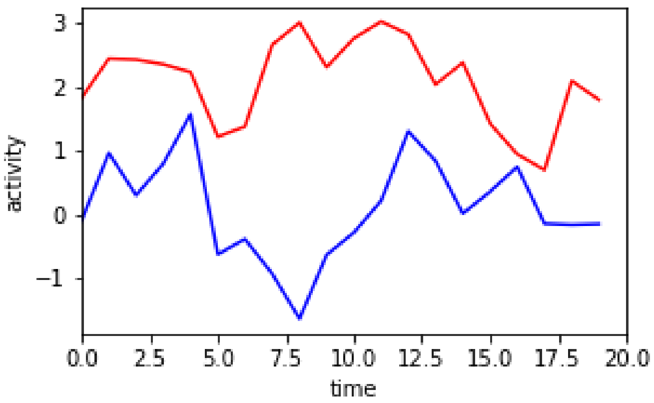


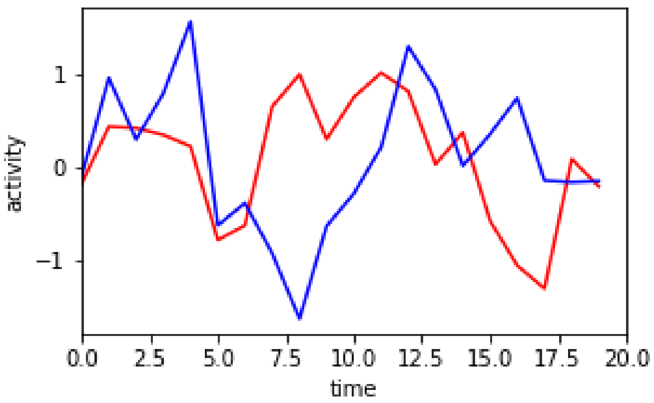
Mode-based approach for classification



Toy model: single autoregressive process

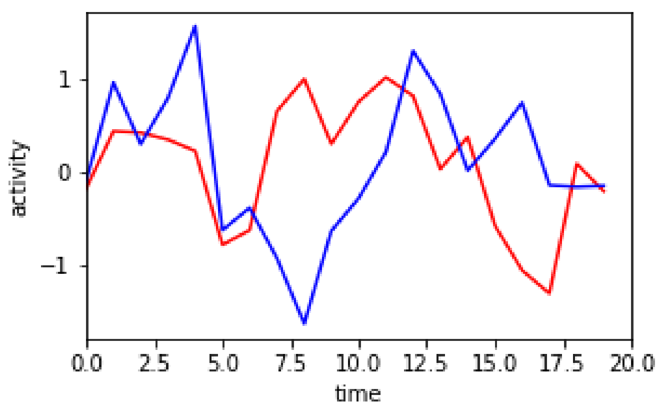
- Discriminate time series: means or second-order statistics?

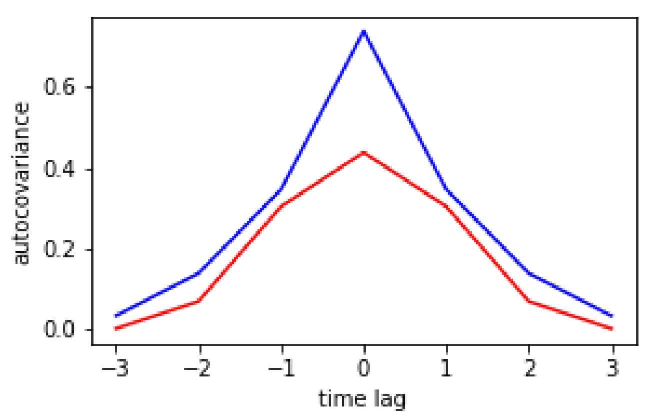




Toy model: single autoregressive process

- Discriminate time series: means or second-order statistics?





Toy model: single autoregressive process

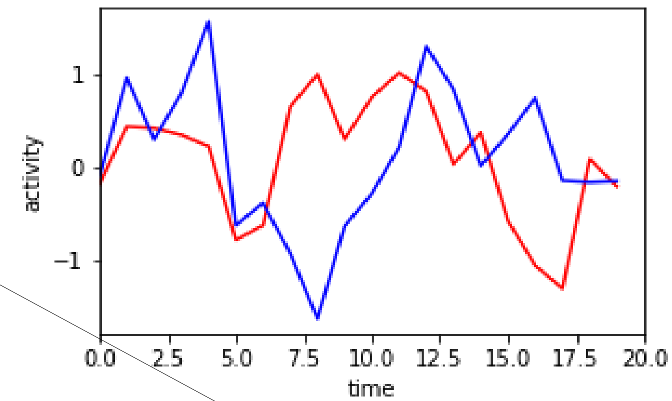
- Discriminate time series: means or second-order statistics?
- Model inversion versus observed covariance

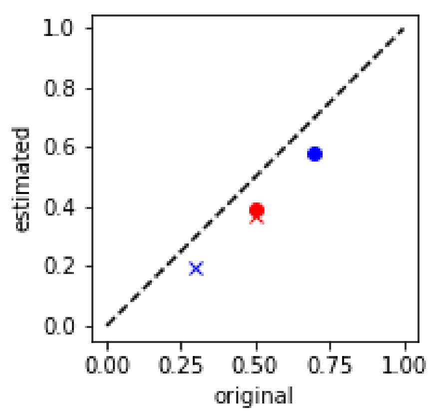
$$x^{t+1} = a\,x^{t} + \zeta^{t}$$

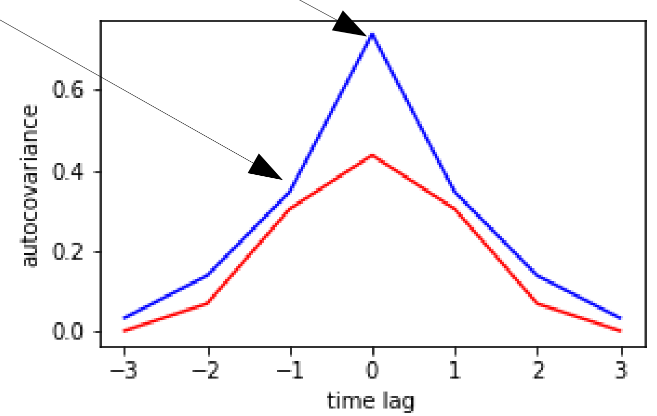
$$s = \langle \zeta^{t} \zeta^{t} \rangle$$

$$c^{0} = \frac{s^{2}}{1-a^{2}}$$

$$c^{1} = a\,c^{0}$$







Toy model: single autoregressive process

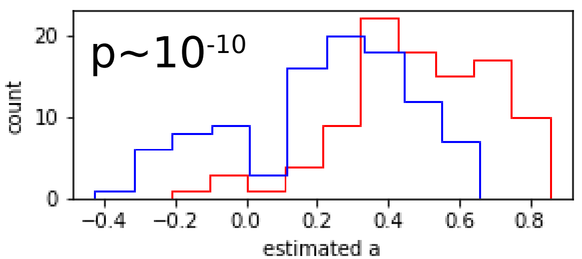
- Discriminate time series: means or second-order statistics?
- Model inversion versus observed covariance

$$x^{t+1} = a\,x^t + \zeta^t$$

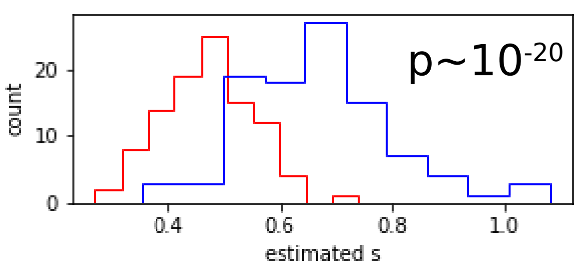
$$s = \langle \zeta^t \zeta^t \rangle$$

$$c^0 = \frac{s^2}{1-a^2}$$

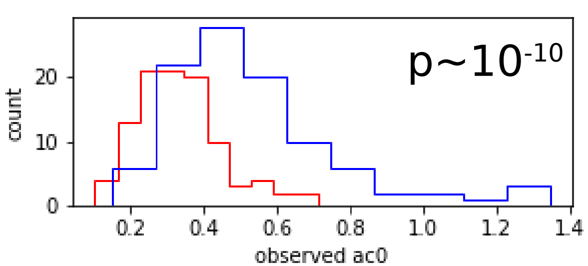
$$c^1 = a\,c^0$$



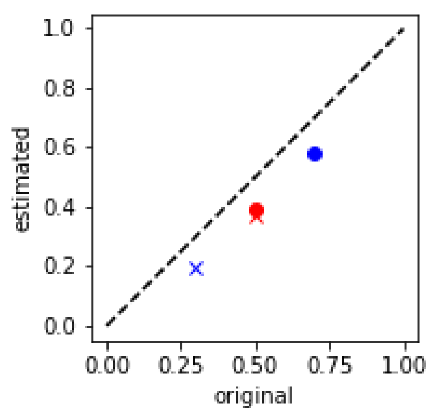
a

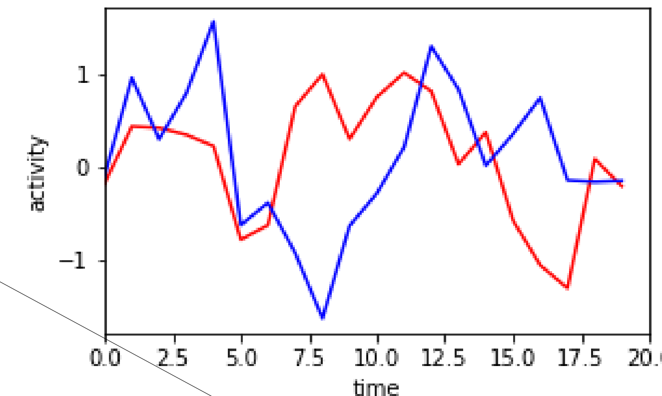


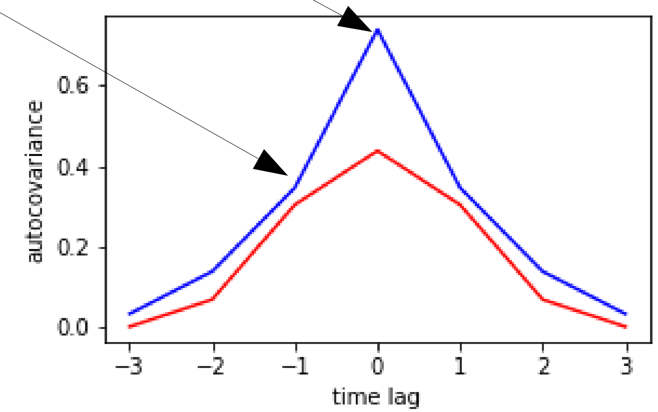
s



c^0







Summary for connectivity measures

- Model as hypothesis on data structure or underlying neuronal dynamics
  - Every connectivity measure implies a model (phenomenological or more mechanistic)
- Value of model
  - Goodness of fit to reproduce data
  - Extracting information from data: biomarker
  - Interpretability: mechanistic explanation of data

Summary for connectivity measures

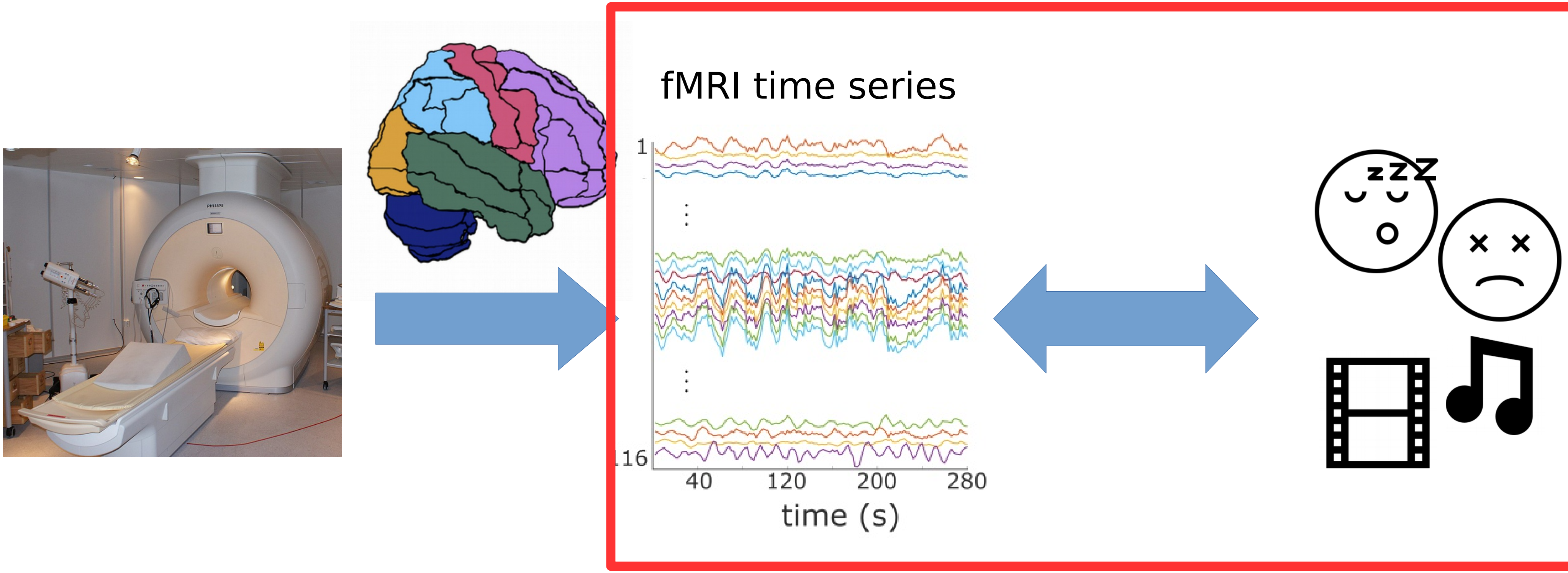
- Model as hypothesis on data structure or underlying neuronal dynamics
  - Every connectivity measure implies a model (phenomenological or more mechanistic)
- Value of model
  - Goodness of fit to reproduce data
  - Extracting information from data: biomarker
  - Interpretability: mechanistic explanation of data
- What is your question?
  - Individualized model for patient
  - Common traits in model for group of subjects to study cognition

Outline

- Connectivity measures for fMRI data
- **Identification of task/subject using EC-based classification**
- Network theory

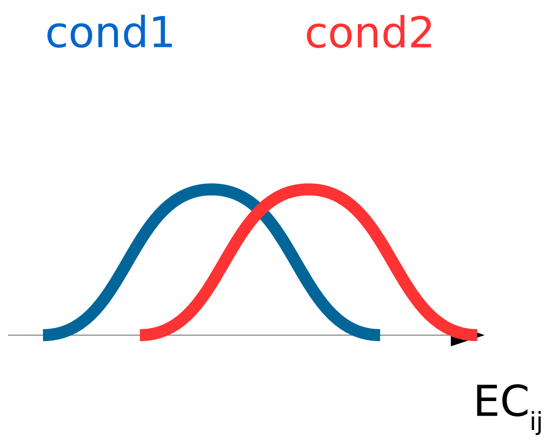
- Reference: Gilson et al. (bioRxiv) “MOU-EC: model-based whole-brain effective connectivity to extract biomarkers for brain dynamics from fMRI data and study distributed cognition”; http://doi.org/10.1101/531830
- Open-access preprints on http://matthieugilson.eu/publications.html
- Code: http://github.com/MatthieuGilson/pyMOU
- HBP collab: http://collab.humanbrainproject.eu/#/collab/48372/

Do connectivity measures capture task-relevant information?

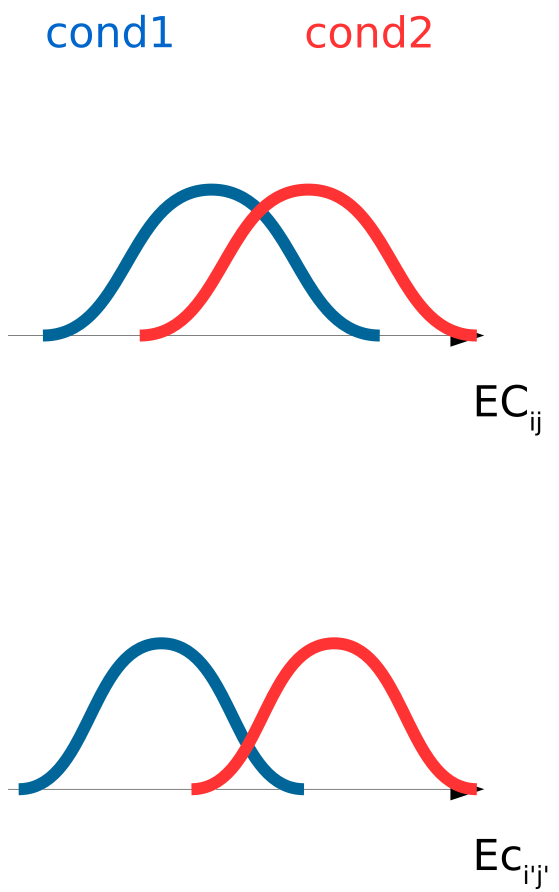


- Classification
- Cross-validation
- Extract biomarker

Statistical testing versus machine learning

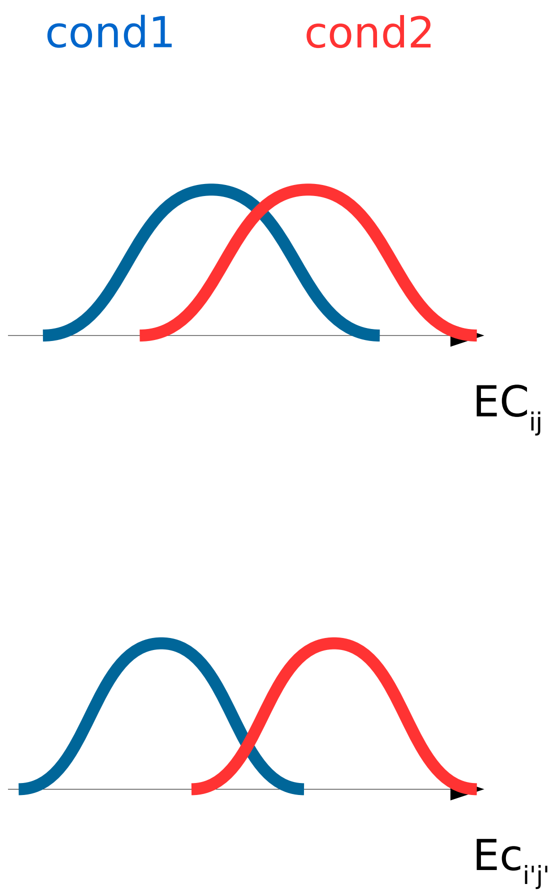


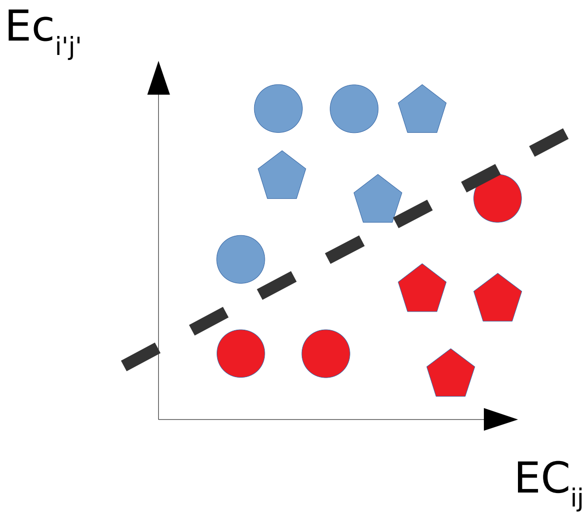
Statistical testing versus machine learning



Multiple comparison correction
for 1000+ weight estimates?

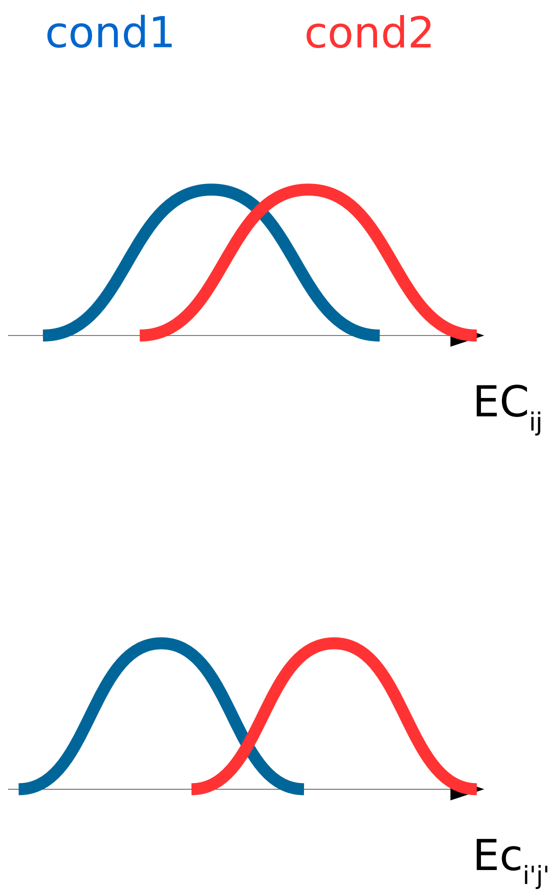
Statistical testing versus machine learning

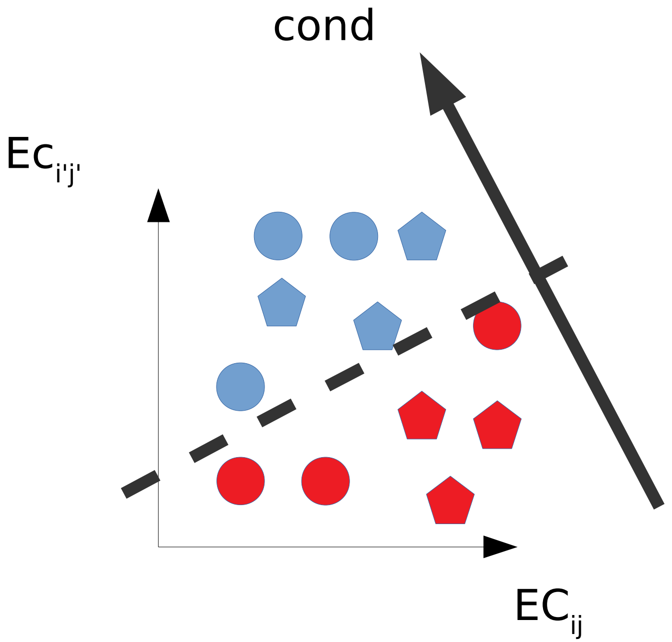




Multiple comparison correction
for 1000+ weight estimates?

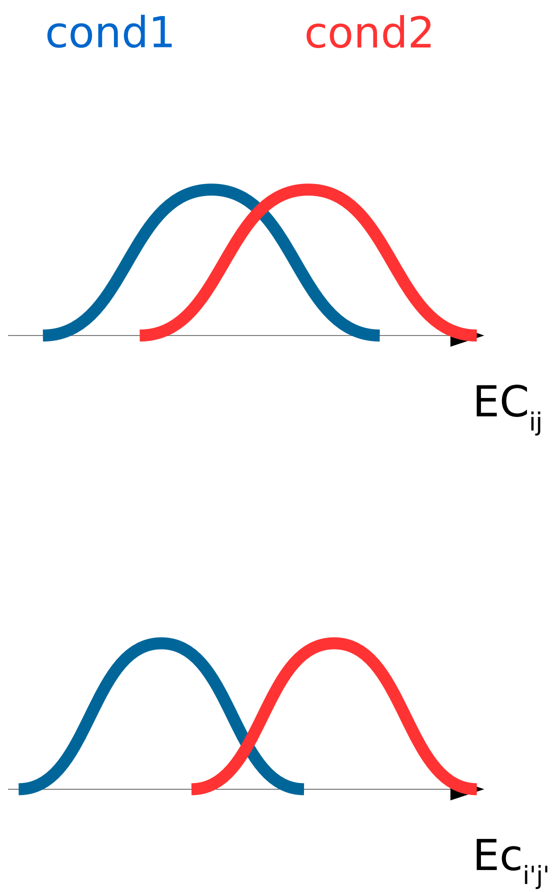
Statistical testing versus machine learning



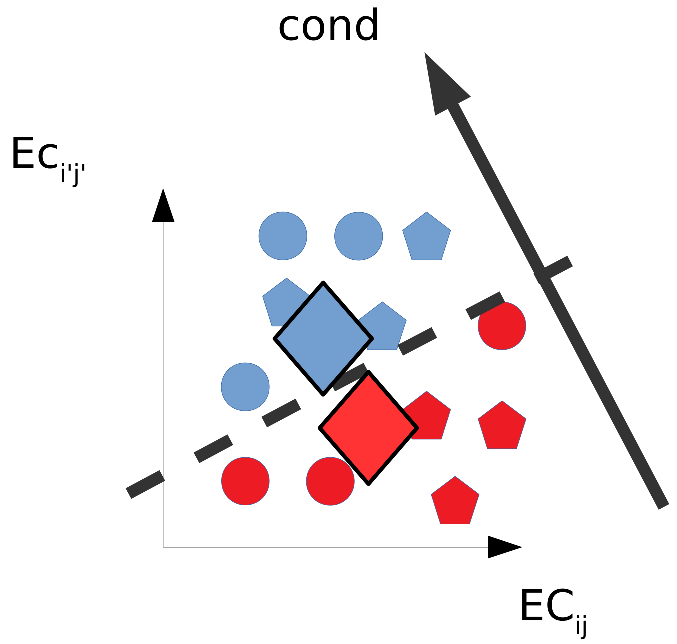


Multiple comparison correction
for 1000+ weight estimates?

Statistical testing versus machine learning

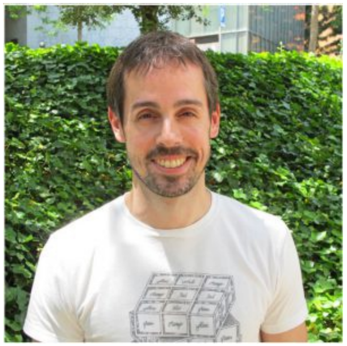


Multiple comparison correction
for 1000+ weight estimates?

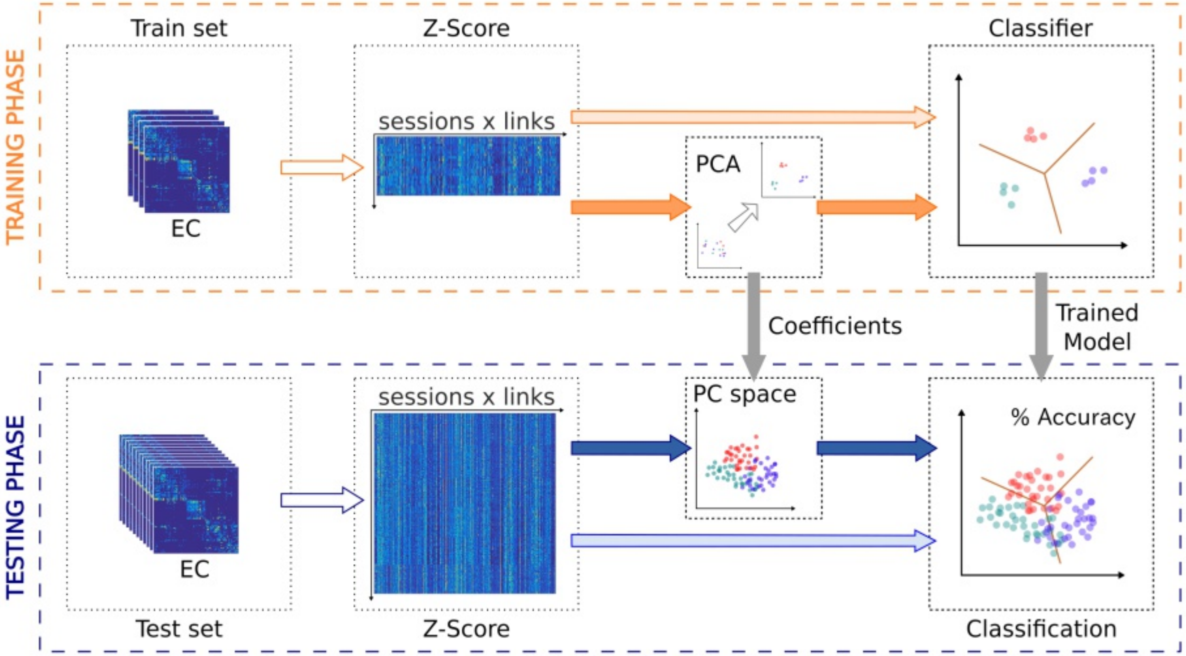


Generalization
over new subjects

Train-test procedure for cross-validation



- **Multinomial linear regression (MLR)**
- 1-nearest-neighbor (1NN)

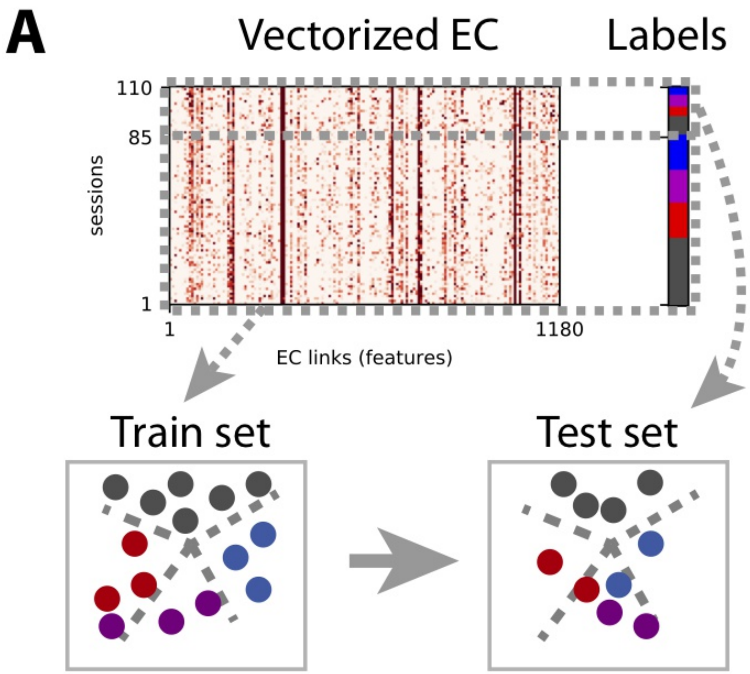


- Data divided in train set and test set
- Calculate accuracy on test set
- Repeat for various splits of data

V Pallarés, A Insabato, A Sanjuan, S Kühn, D Mantini, G Deco, M Gilson (2018) Neuroimage

Varoquaux et al. Neuroimage 2018; Python library scikit-learn (Thirion's team in SP2)

Classification of tasks



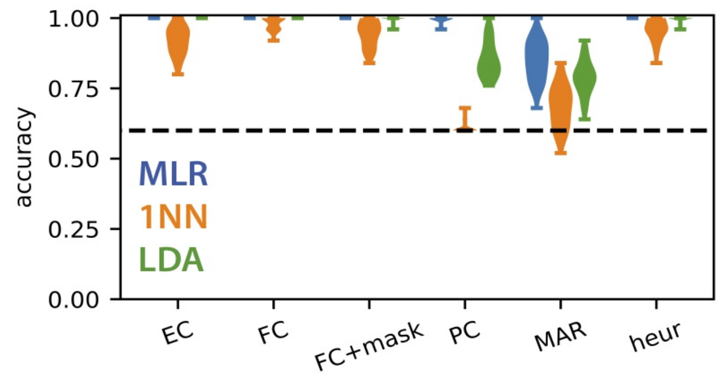
- Data from D Mantini and M Corbetta (Hlinka et al. Neuroimage 2011)
- 22 subjects
- 5 sessions/runs:
  - 2 for rest
  - 3 for movie viewing (distinct parts of movie)

Gilson et al. bioRxiv

Classification of tasks

- Movie viewing versus rest is easy: almost any connectivity measure works

B 2-task identification (movie versus rest)

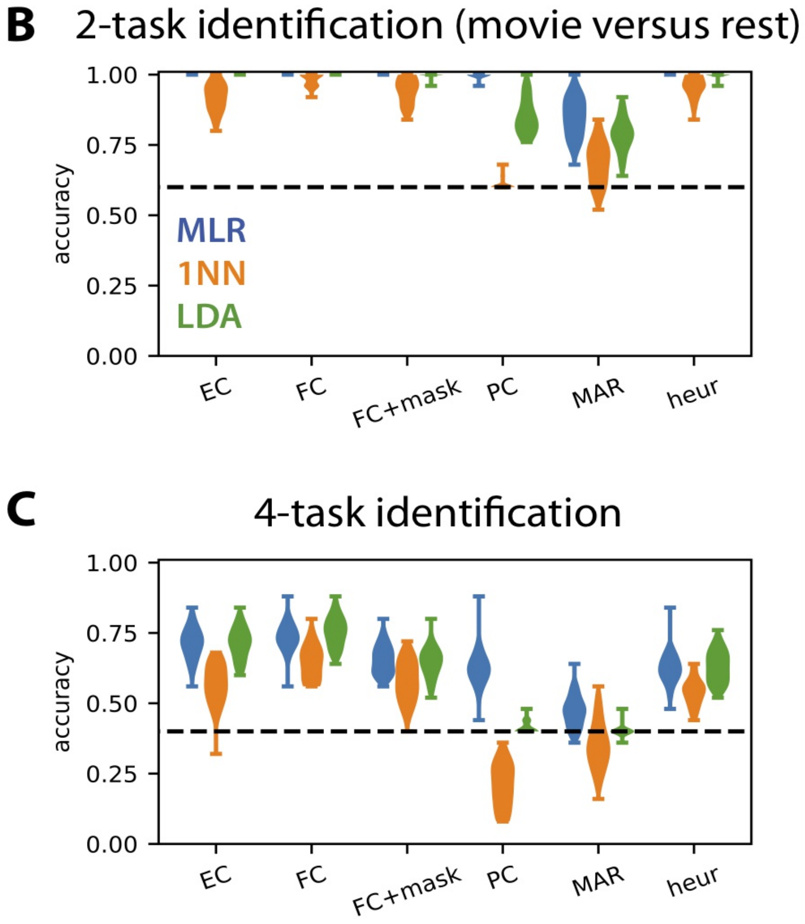


Gilson et al. bioRxiv

Classification of tasks

- Movie viewing versus rest is easy: almost any connectivity measure works

- Rest, M1, M2 and M3: more difficult: EC and FC work best

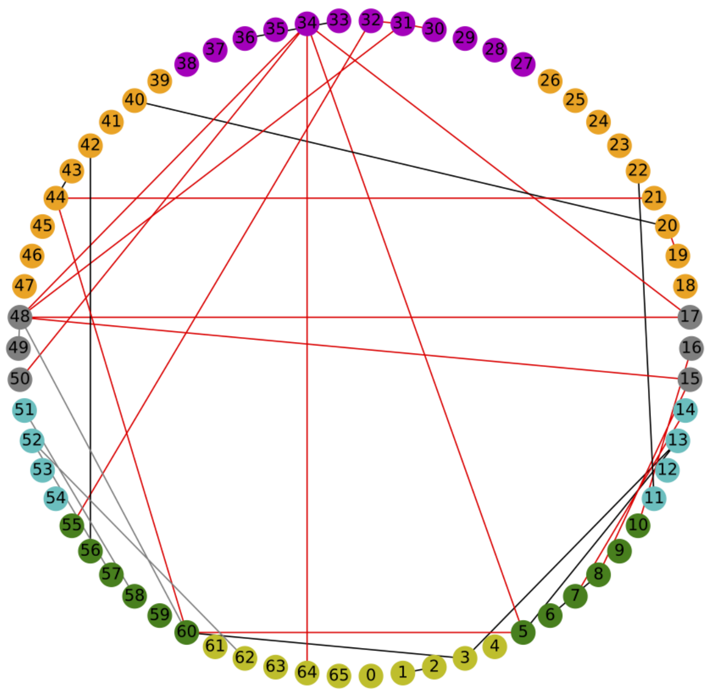


Gilson et al. bioRxiv

Biomarker: signature subnetwork

- Informative EC/FC links that support correct classification

A Support network of informative links



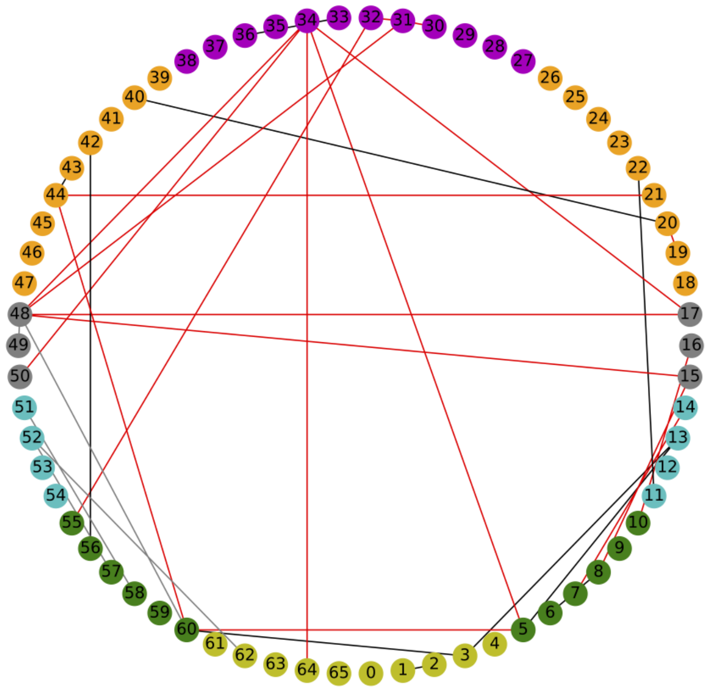
gray: 2 tasks only (rest versus movie)
black: 2 tasks and 4 tasks
red: 4 tasks only

Gilson et al. bioRxiv

Biomarker: signature subnetwork

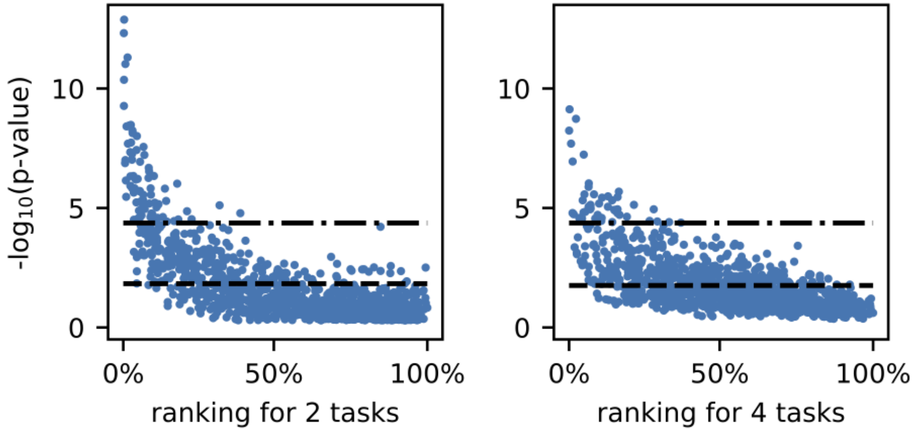
- Informative EC/FC links that support correct classification
- Machine learning well suited for multivariate features (connectivity) and multiple labels (conditions)

A Support network of informative links



gray: 2 tasks only (rest versus movie)
black: 2 tasks and 4 tasks
red: 4 tasks only

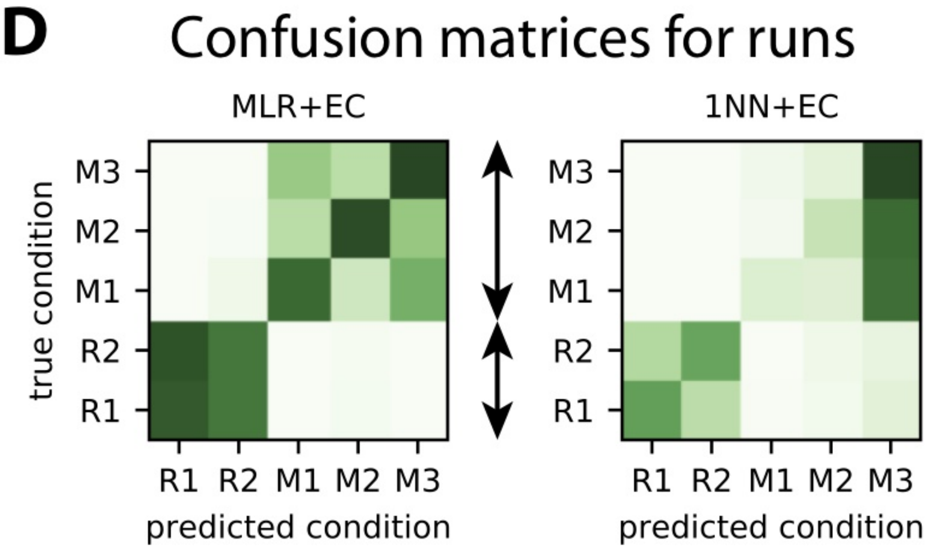
B Classification ranking versus statistical significance



Gilson et al. bioRxiv

Hierarchy of cognitive tasks

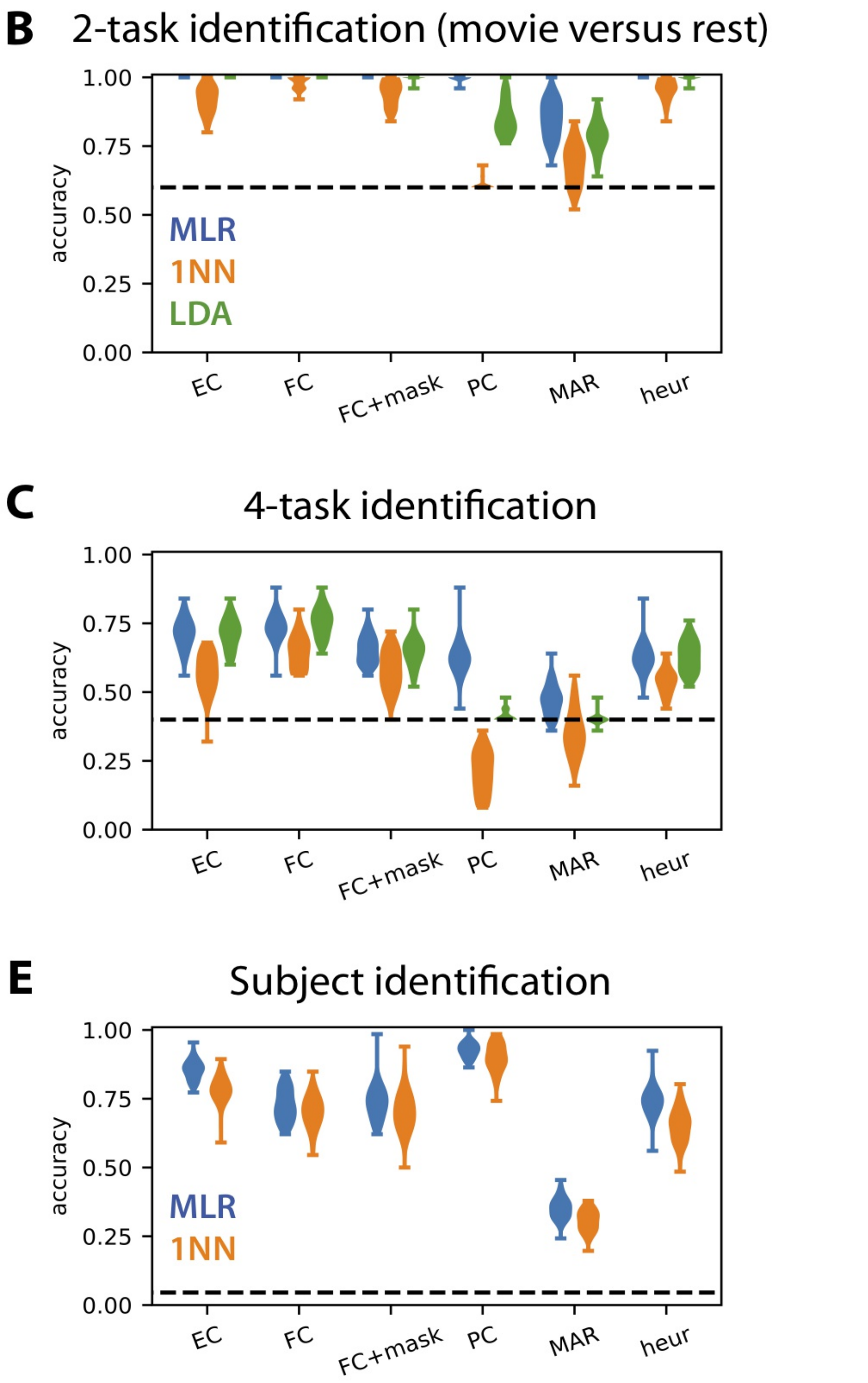
- Mapping structure of connectivity measure with structure of cognitive states
- See also unsupervised techniques (clustering)



Gilson et al. bioRxiv

Classification of subjects

- Movie viewing versus rest is easy: almost any connectivity measure works
- Rest, M1, M2 and M3: more difficult: EC and FC work best
- Subjects: EC and PC work best

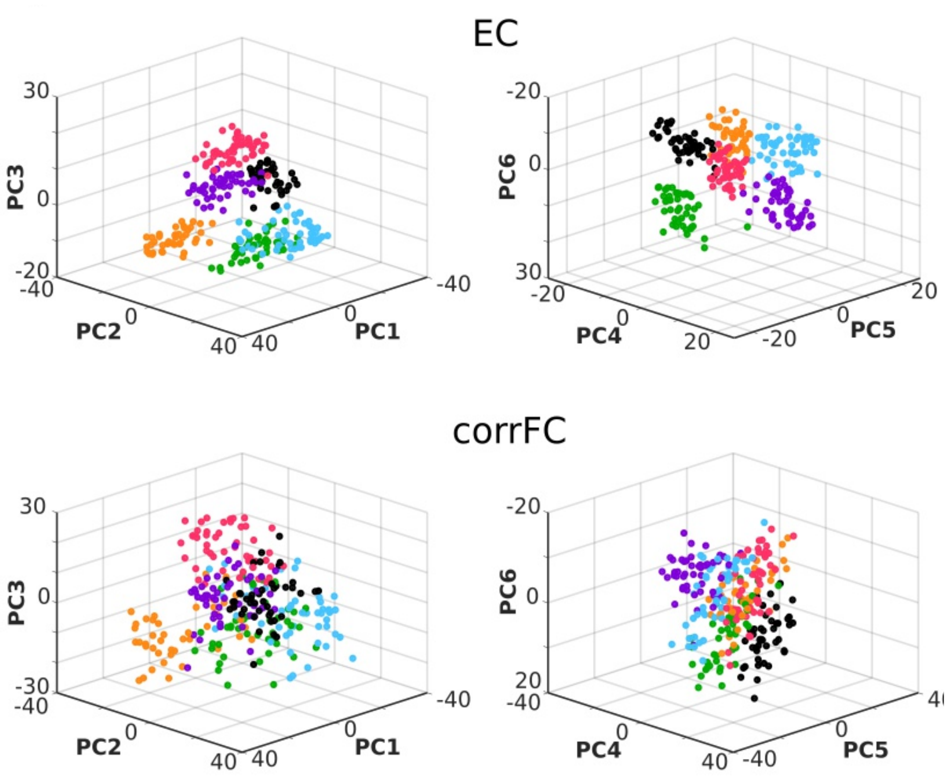


Gilson et al. bioRxiv

EC/FC as individual fingerprint

- Data from Simone Kühn
- 6 healthy subjects, 50 sessions

- EC is better than FC for discriminating subjects using resting-state fMRI
  - more robust to day-to-day variability

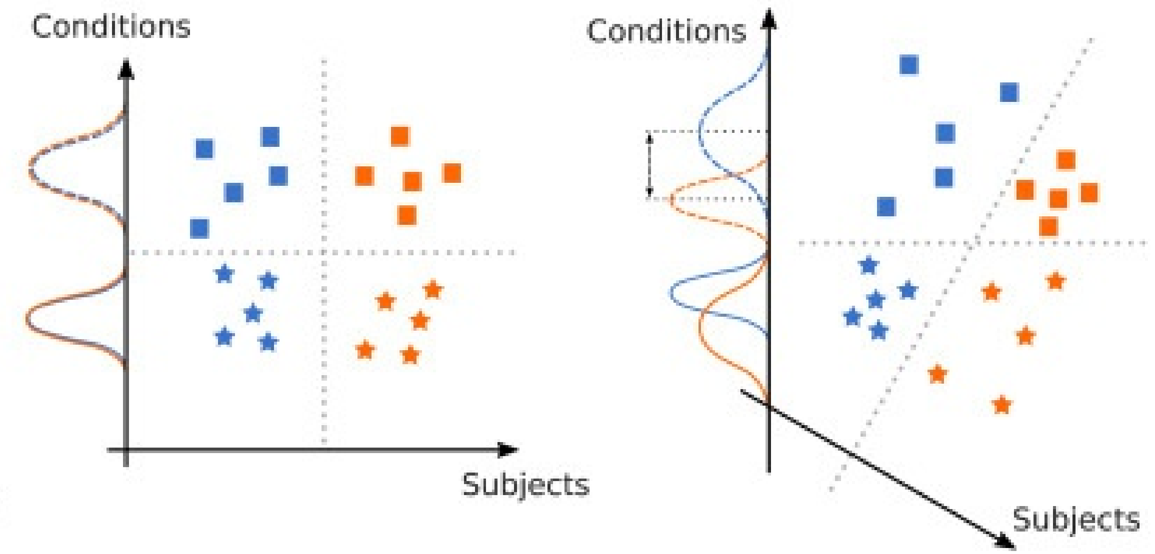


Subject identification:
- Finn et al. (2015) Nat Neurosci;
- special issue “Individual Subject Prediction” in Neuroimage

V Pallarés et al., Neuroimage 2018

Twofold classification subject-task

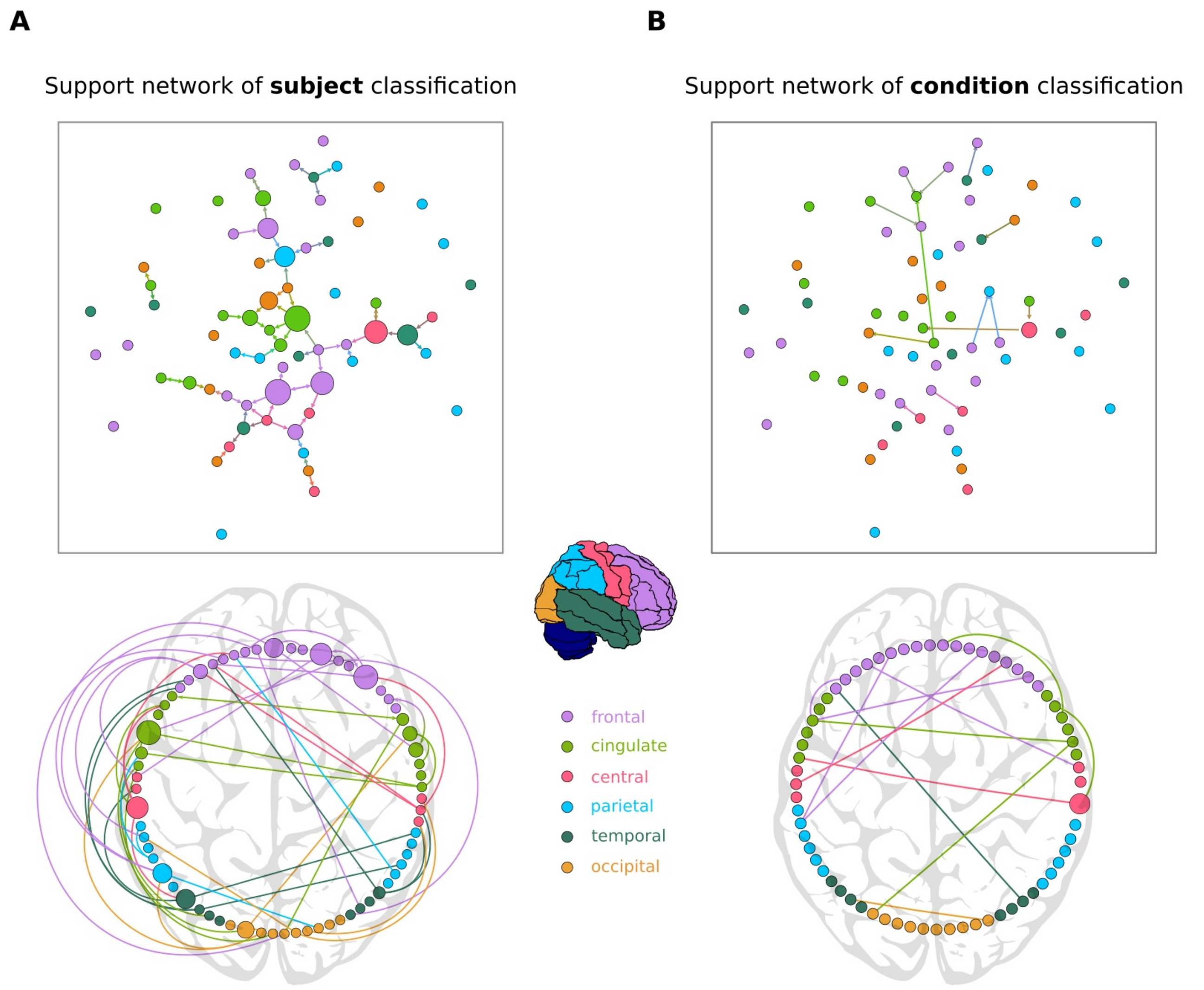
- BOLD signals are contaminated by individual traits
- Issue when datasets involve distinct subjects (distinct cohort for healthy control and neuropathology)
- But even in general with same subjects



V Pallarés, A Insabato, A Sanjuan, S Kühn, D Mantini, G Deco, M Gilson
Neuroimage 2018

Twofold classification subject-task

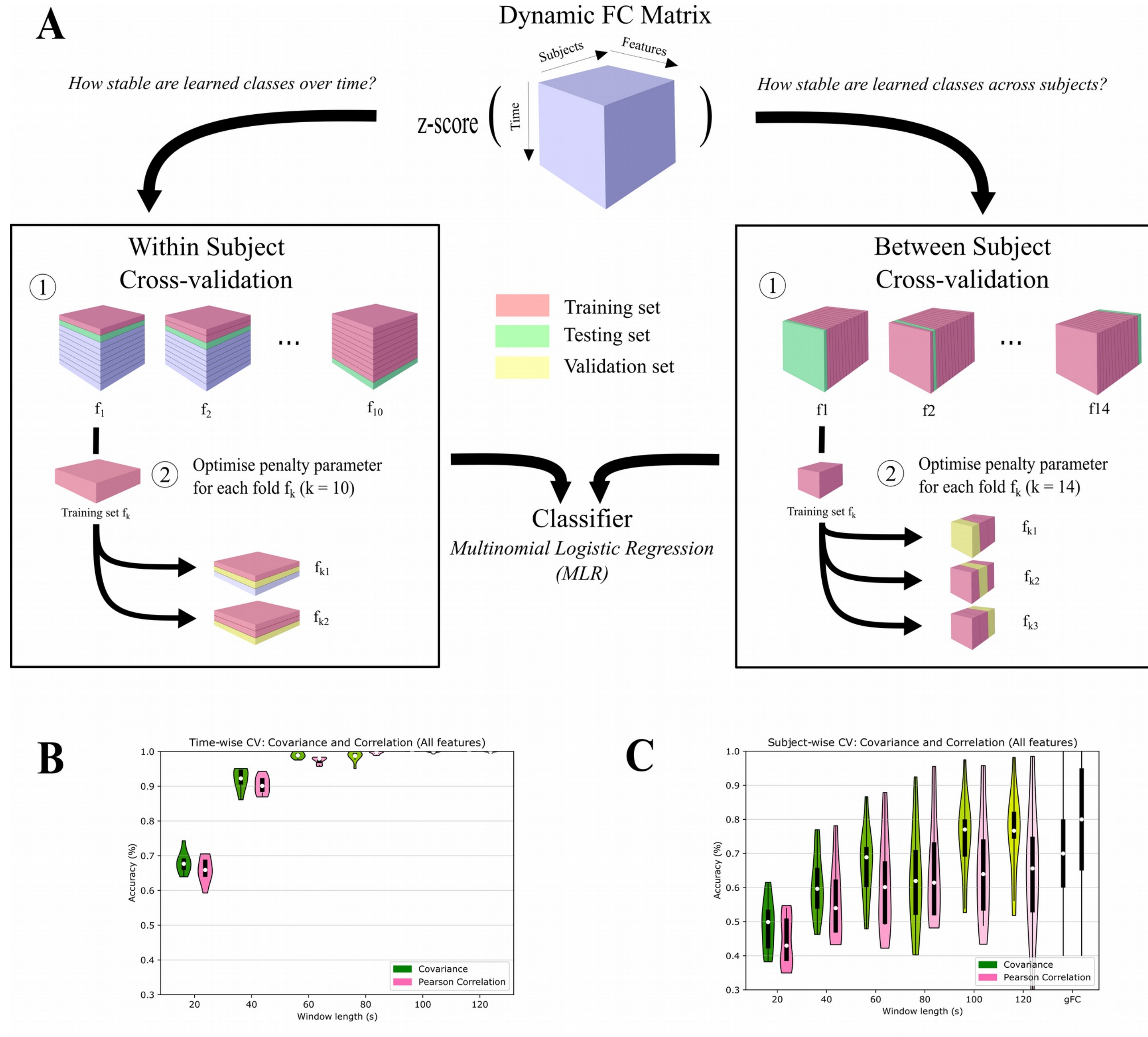
- Task: movie viewing versus rest
- “Orthogonality” between support networks: statistical test for overlap
- Mainly inter-hemispheric EC links for tasks, many links within left hemisphere for subjects



V Pallarés, A Insabato, A Sanjuan, S Kühn, D Mantini, G Deco, M Gilson
Neuroimage 2018

Other dataset with 4 tasks + rest

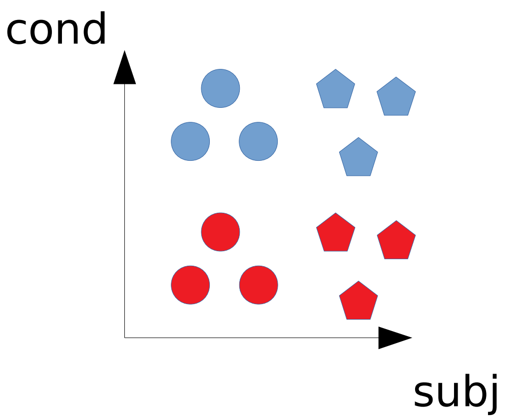
- To mix or not to mix subject information in train and test sets
- Beware of inflated results for classification!



S Benitez-Stulz et al., submitted

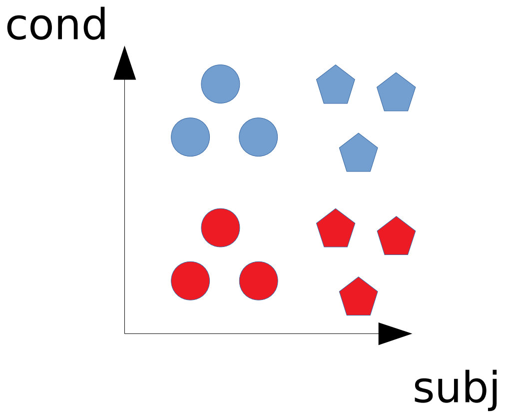
Take-home messages for classification

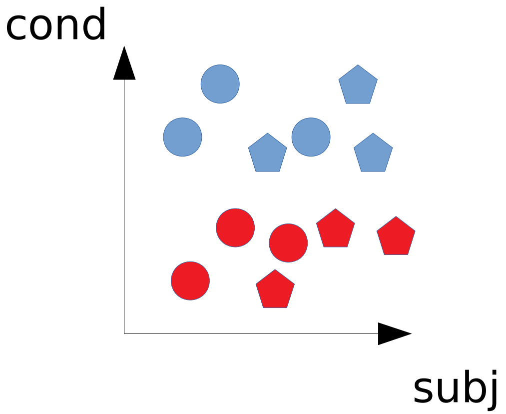
- Need adequate method to disentangle contributions from subject variability and condition variability



Take-home messages for classification

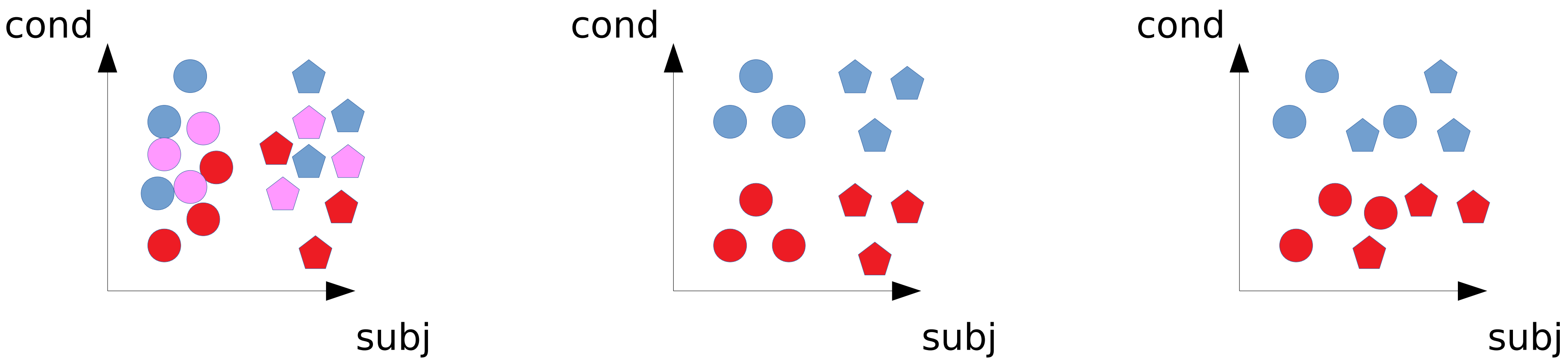
- Need adequate method to disentangle contributions from subject variability and condition variability





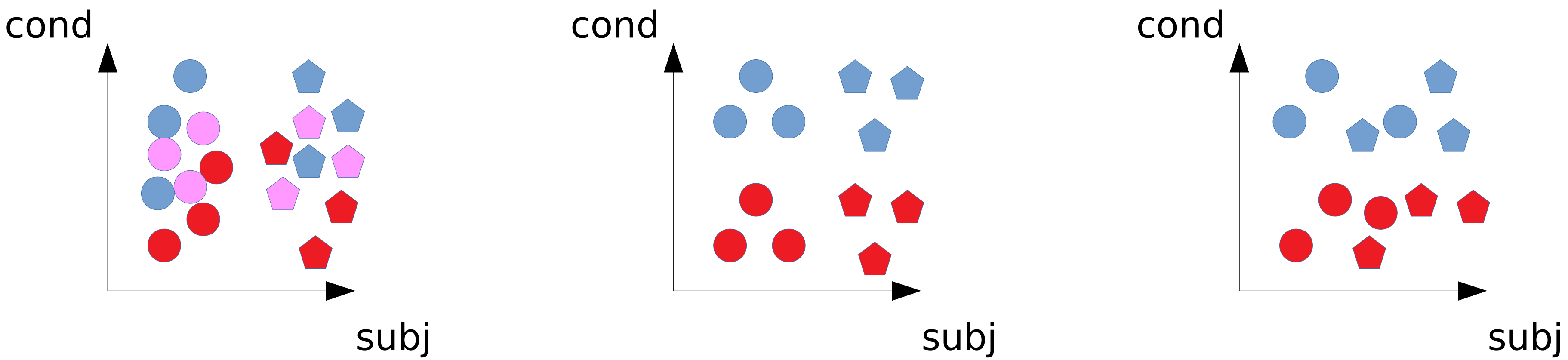
Take-home messages for classification

- Need adequate method to disentangle contributions from subject variability and condition variability



Take-home messages for classification

- Need adequate method to disentangle contributions from subject variability and condition variability



- Temporal information matters (EC for subject identification)
- Connectivity measures should be benchmarked with many task conditions to verify generalization capability
- Adequate classifier (MLR good for feature selection) and cross-validation method

Current biomarkers and future improvements

wikipedia

Current biomarkers and future improvements

wikipedia

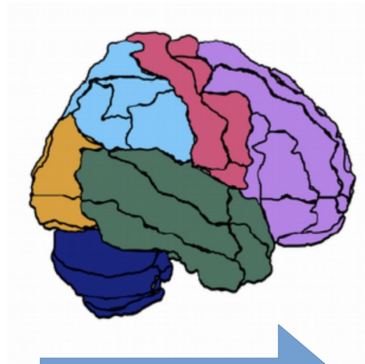
Current biomarkers and future improvements

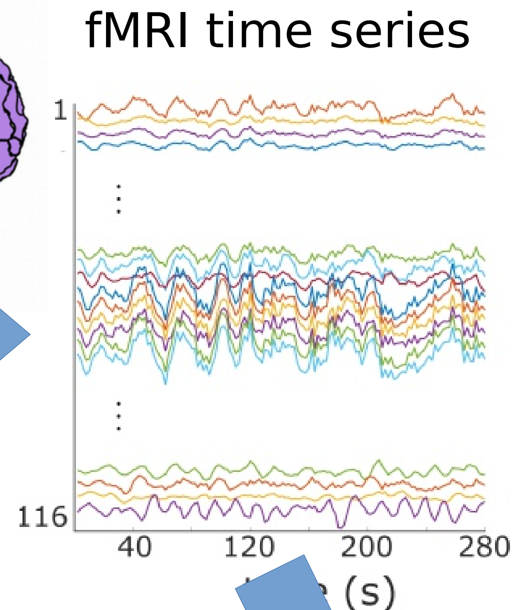
Outline

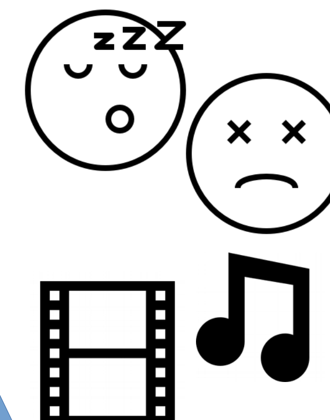
- Connectivity measures for fMRI data
- Identification of task/subject using EC-based classification
- **Network theory**

- Reference: Gilson et al. (bioRxiv) “MOU-EC: model-based whole-brain effective connectivity to extract biomarkers for brain dynamics from fMRI data and study distributed cognition”; http://doi.org/10.1101/531830
- Open-access preprints on http://matthieugilson.eu/publications.html
- Code: http://github.com/MatthieuGilson/pyMOU
- HBP collab: http://collab.humanbrainproject.eu/#/collab/48372/

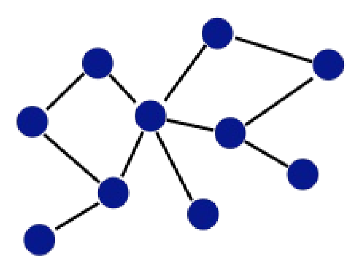
Network metrics as summaries of connectivity







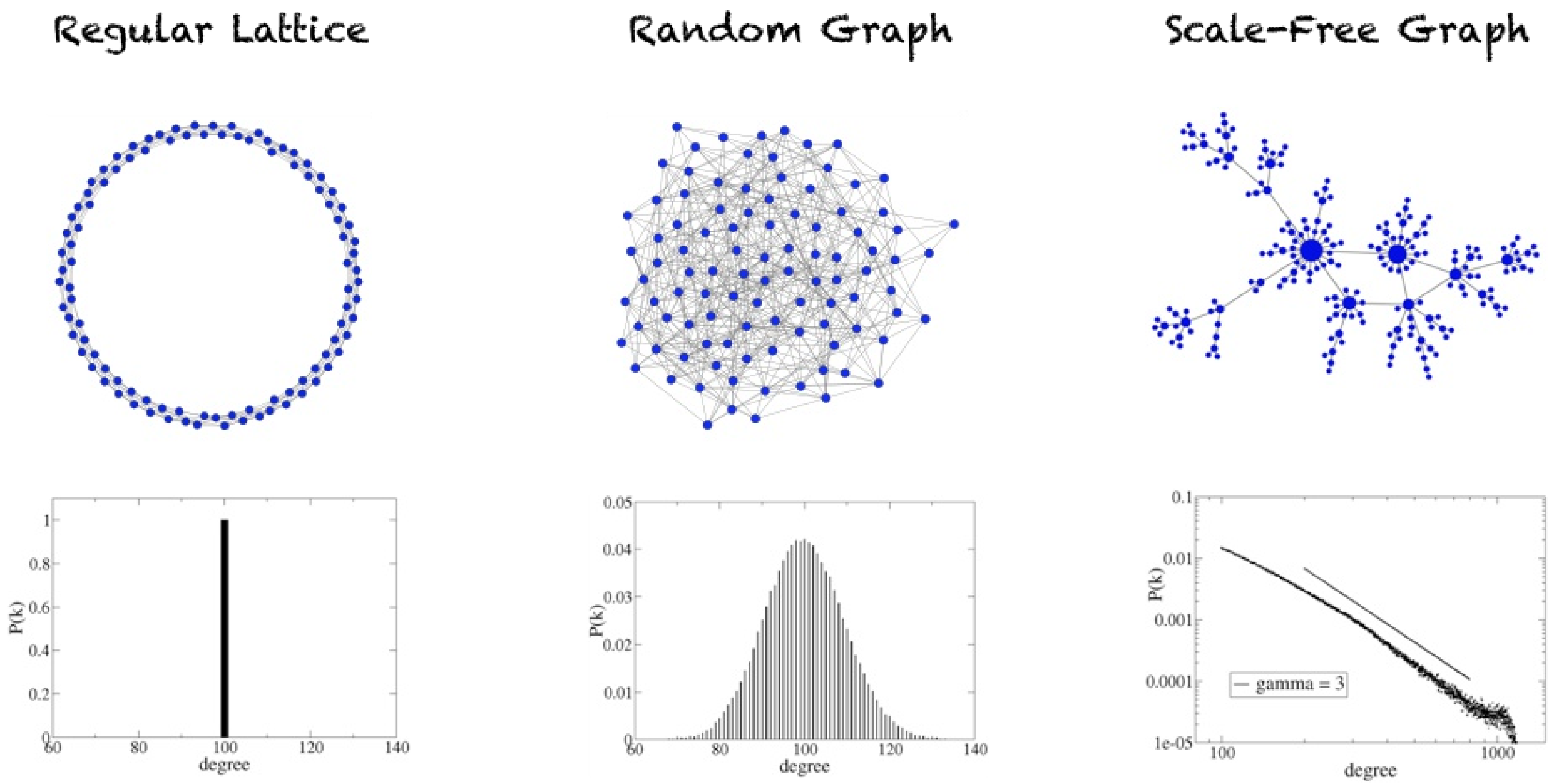
graph



- clustering
- complexity measure
- etc.

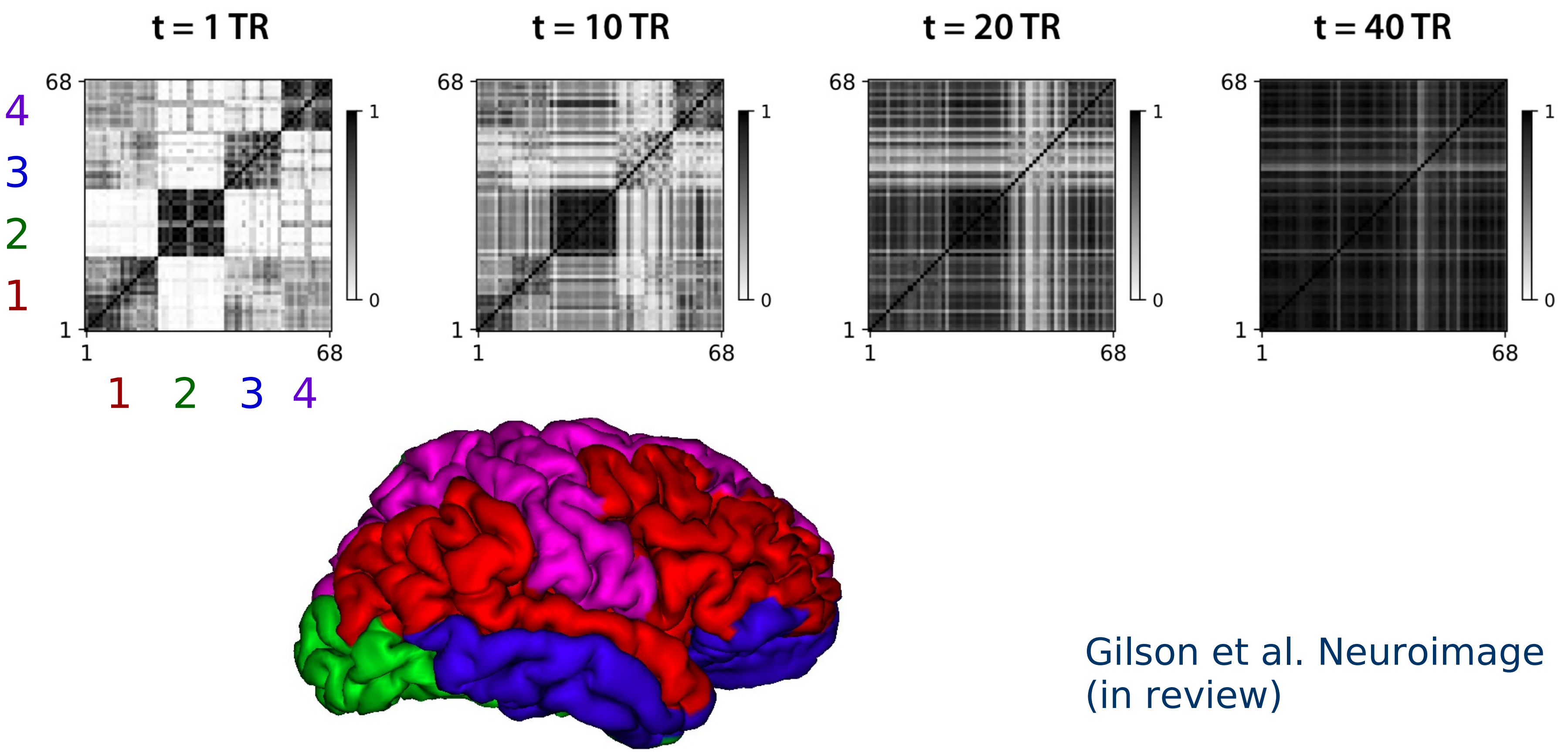
Network theory

- Gorka Zamora-López: Galib Python library
- Compare network from data with references



Network theory for MOU-EC

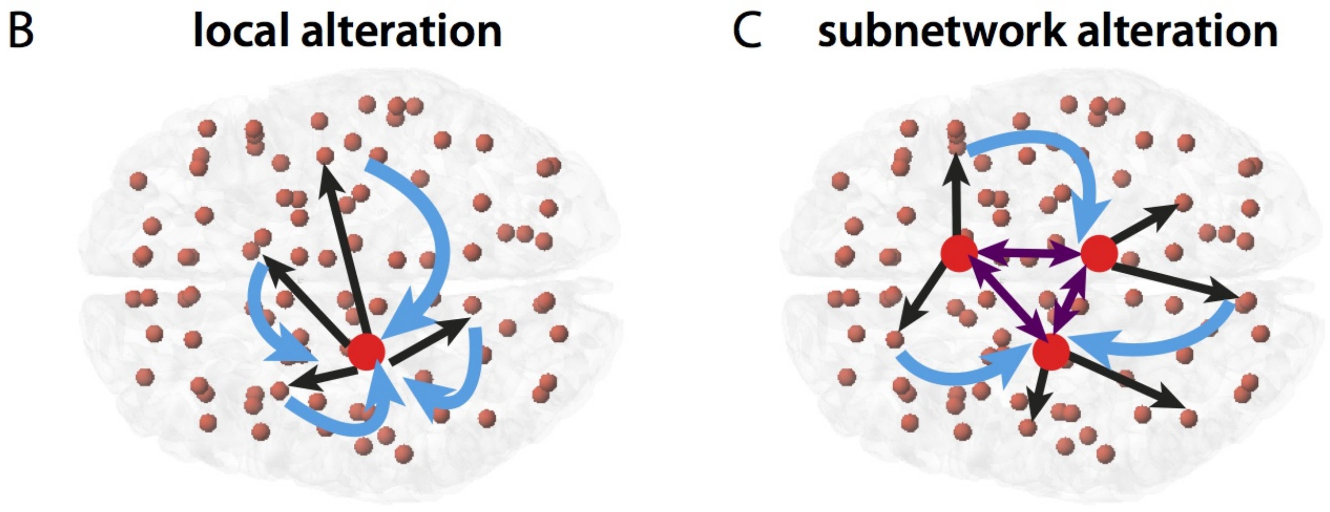
- Detect communities in brain network
- Merging of communities following perturbation (stimulation)
  - from segregated to global integration



Gilson et al. Neuroimage
(in review)

Toolbox for whole-brain fMRI analysis

- Interesting playground provided by fMRI: dynamics (estimation), statistics / machine learning (classification), network theory
  - Linear algebra: well adapted for large networks
- Quantitative characterization of brain "states"
- Network-oriented analysis, suitable for large datasets
- Application to cognition (SP2-SP3) and neuropathologies (SP8)



Code: http://github.com/MatthieuGilson/pyMOU

HBP collab: http://collab.humanbrainproject.eu/#/collab/48372/

upf. Universitat Pompeu Fabra Barcelona

European Commission

Human Brain Project

MARIE CURIE ACTIONS