Beyond classical connectivity analysis: Inspecting temporal variability in brain functional connectivity

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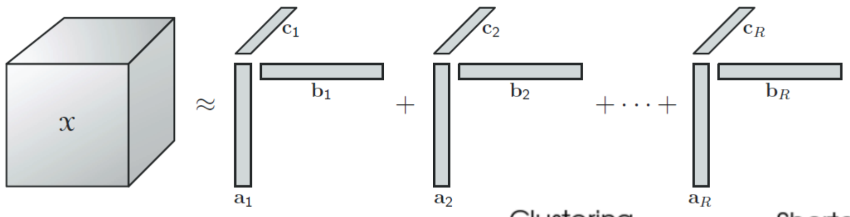
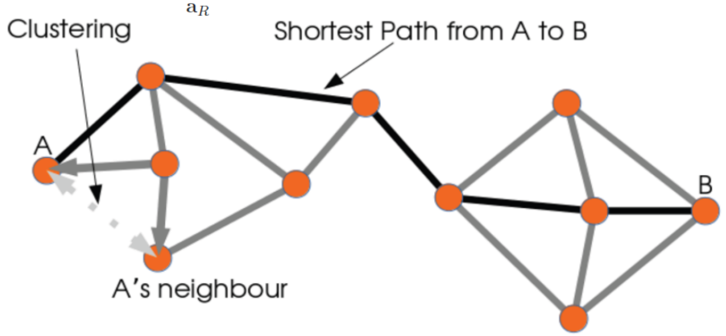
Contents (I)

- Special interest in brain activity and monitoring of disease
  - Electrophysiology (EEG)



- (Dynamic) brain connectivity
  - Multiway analysis techniques
  - Network analysis and related techniques



Contents (II)

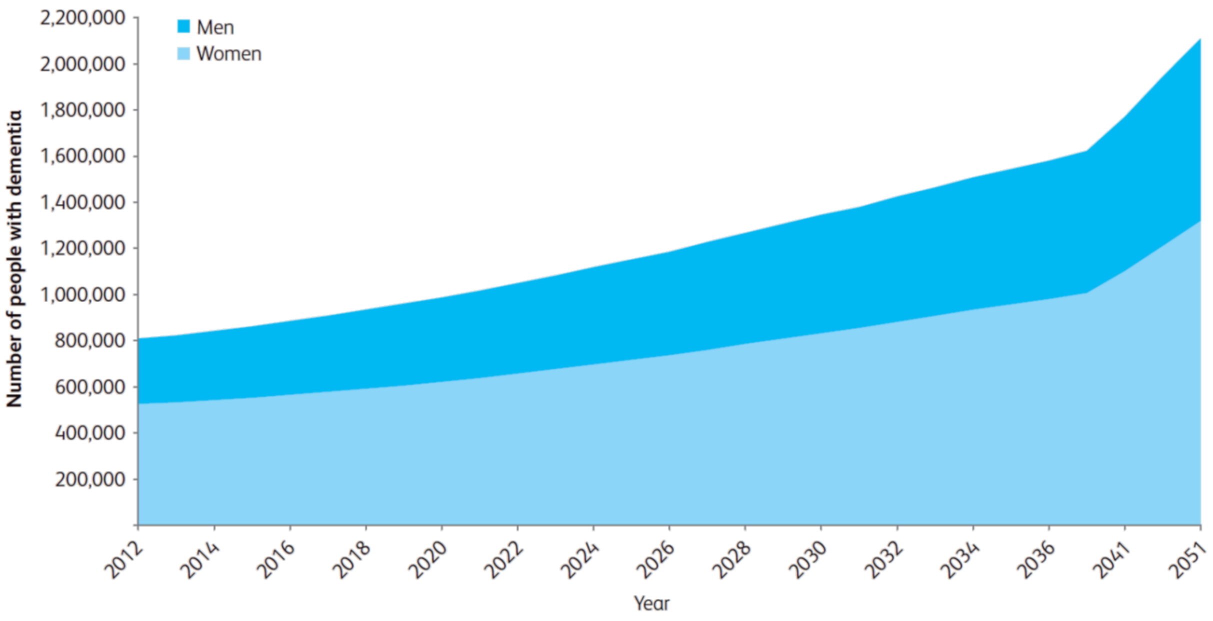
- Background
- Network analysis towards dynamic connectivity
- Vision
- Tensor factorisation
- Signal processing on graphs
- Conclusions

Background

Alzheimer’s disease (AD)

- Most common form of dementia in the Western world
- 1 out of 14 people aged 65 years and over has dementia
- Prevalence roughly doubles every 5 years of age
- The total cost of dementia to society in the UK: ~ £26bn

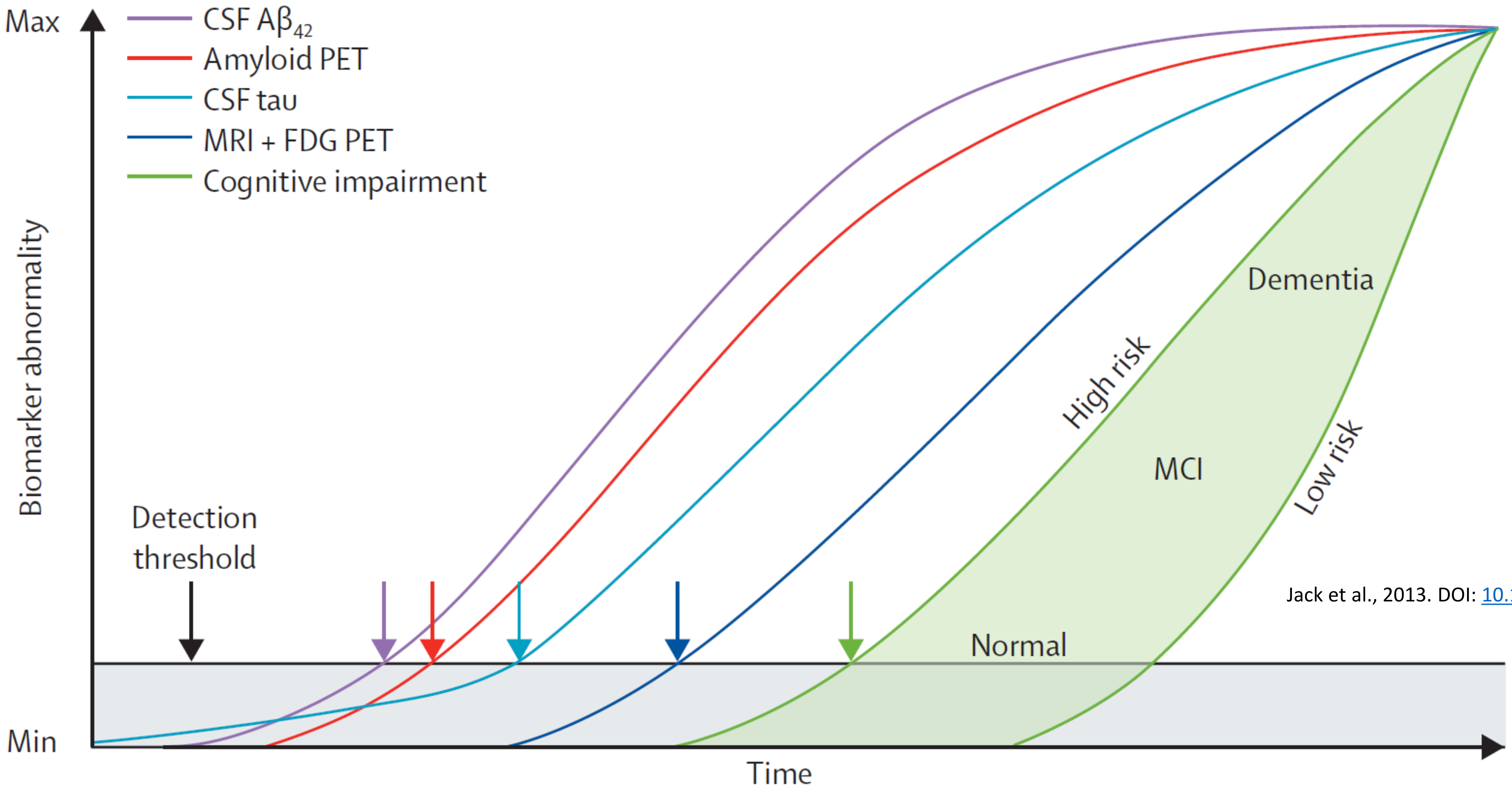
Figure C: Projected increases in the number of people with dementia in the UK, by gender (2012–2051)



https://www.alzheimers.org.uk/download/downloads/id/2323/dementia_uk_update.pdf

Markers of AD

- Complex disease → Mild Cognitive Impairment (MCI)



Jack et al., 2013. DOI: [10.1016/j.neuron.2013.12.003](https://doi.org/10.1016/j.neuron.2013.12.003)

Electroencephalogram (EEG)

- Direct and non-invasive multichannel recording of brain activity
- Advantages
    - High temporal resolution
        - Low spatial resolution
    - Affordable
    - Portable

EEG in AD

- EEG features in AD
  - Spectral
  - Non-linear
  - Connectivity

Neurobiology of Aging 34 (2013) 2023–2036

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

ELSEVIER

Review

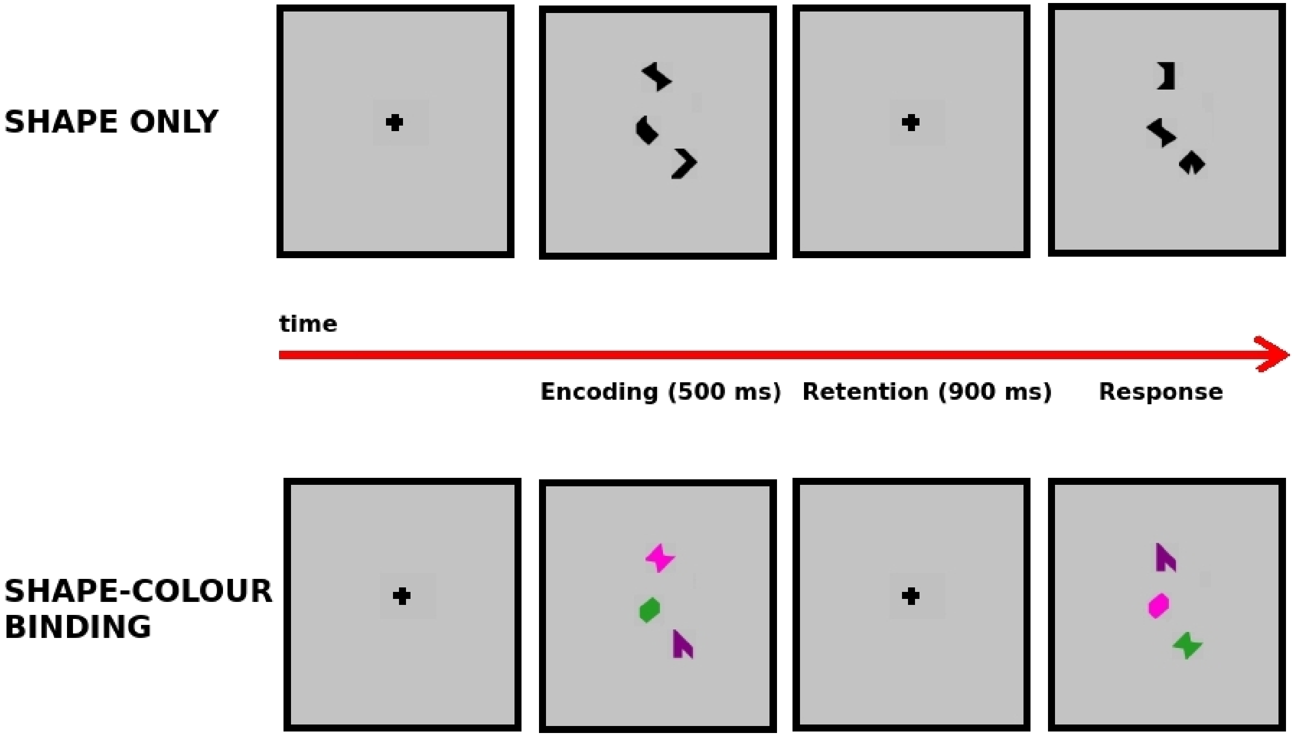
Alzheimer's disease: connecting findings from graph theoretical studies of brain networks

Betty M. Tijms [a,*], Alle Meije Wink [b], Willem de Haan [a], Wiesje M. van der Flier [a,c], Cornelis J. Stam [d], Philip Scheltens [a], Frederik Barkhof [b]

- Prominent role of connectivity
  - Functional connectivity breaks down in AD
- Resting state → Appealing but also limited in some sense
  - Sensitive, not specific yet
  - Contradictory findings? / Classic approaches not enough?

Visual short-term memory binding (VSTMB)

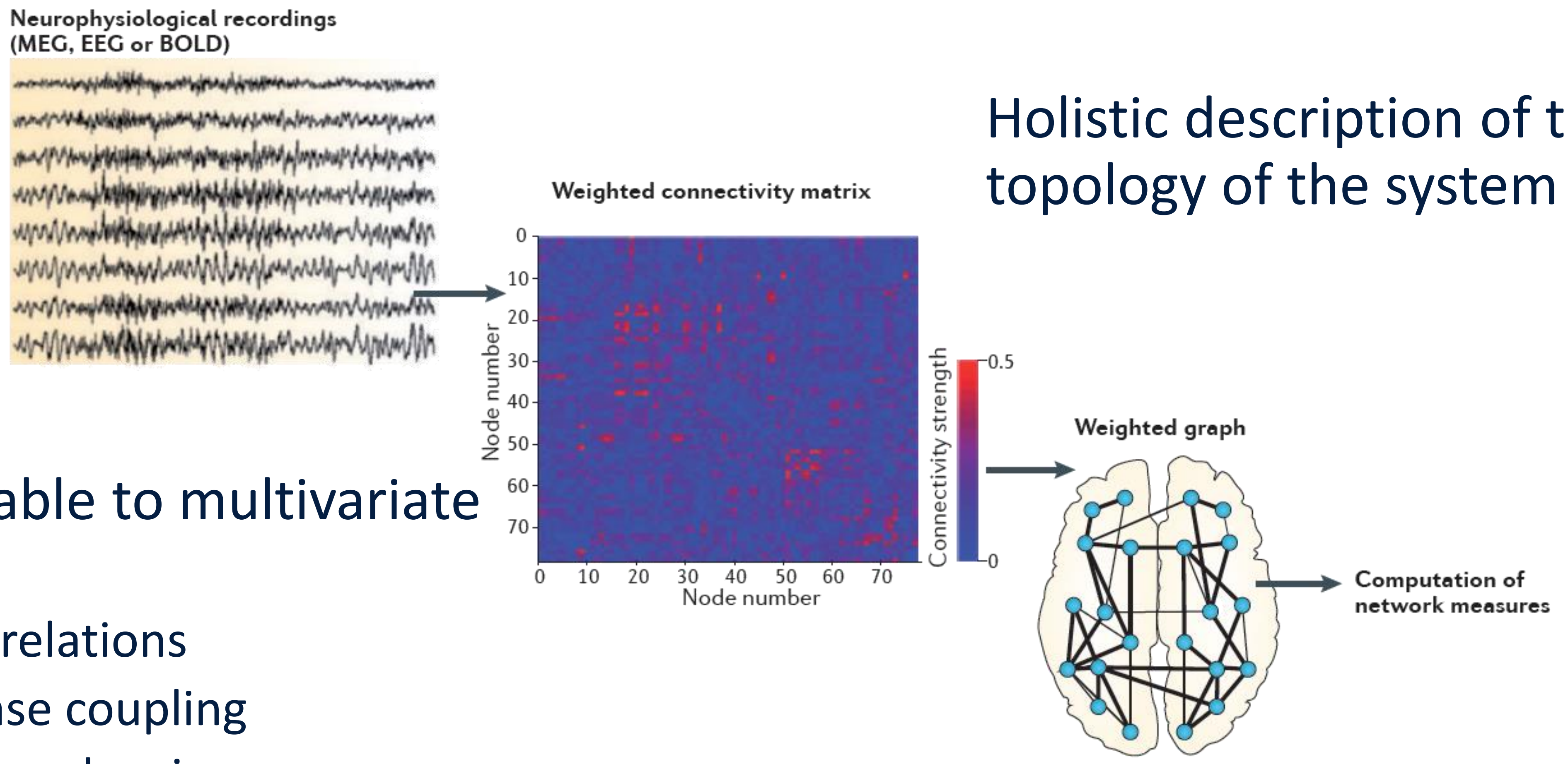
- Deficits present during asymptomatic period
  - Early and specific AD marker
- MCI patients
  - ↓ task performance
- Electrophysiology ↔ Task performance



Pietto *et al.*, 2016, [10.3233/JAD-160056](10.3233/JAD-160056)

Network analysis towards dynamic connectivity

Functional connectivity & Network analysis

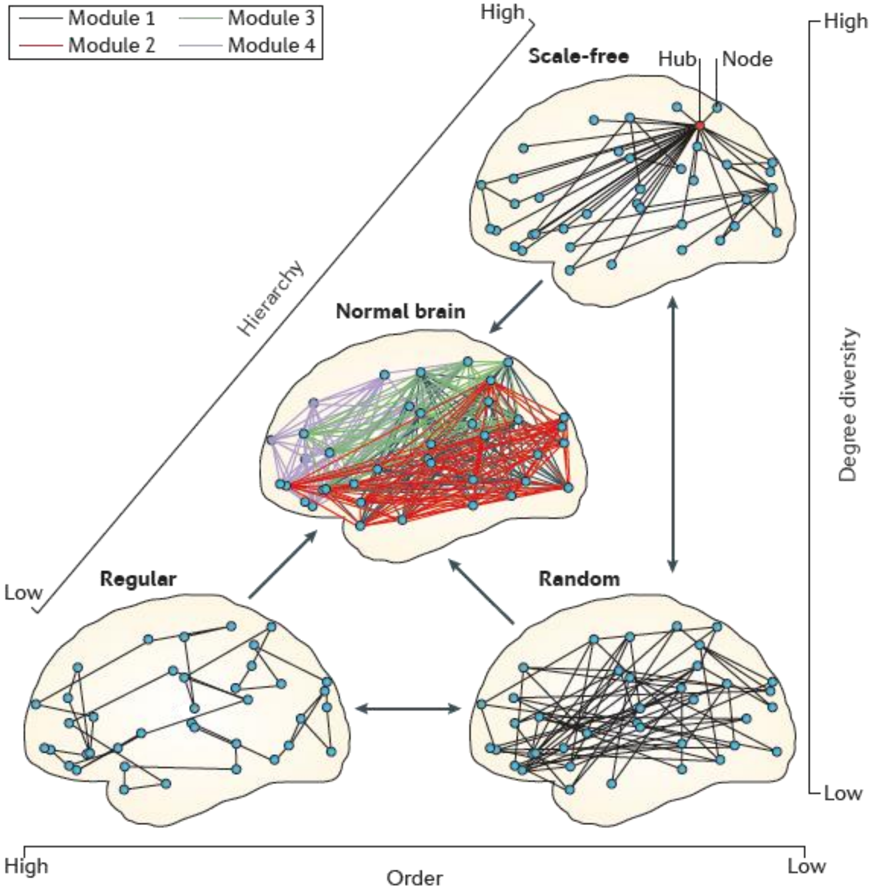


Holistic description of the topology of the system

- Applicable to multivariate data
    - Correlations
    - Phase coupling
    - Dependencies…

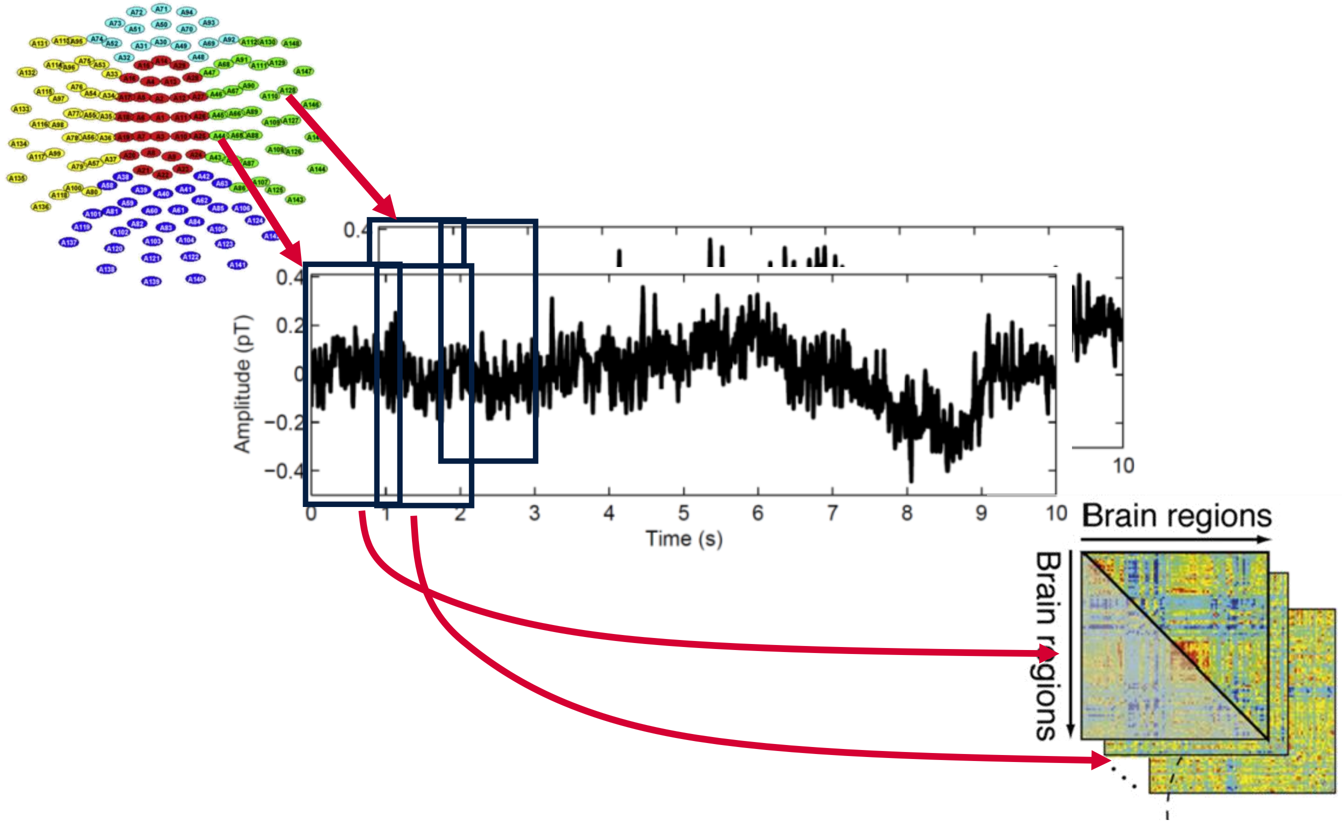
Stam, 2014, DOI: [10.1038/nrn3801](10.1038/nrn3801)

Particularities of brain networks



Stam, 2014, DOI: 10.1038/nrn3801

- Dynamic brain connectivity



Variability in connectivity

- "Dynamic" connectivity explored in fMRI studies
  - Relevant for "fast" EEG (but smaller evidence)
- Pilot assessment of the variability of short-time resting-state
  - EEG dynamical connectivity in AD
- Implications
  - Potential markers of disease
  - Different processes involved in (fast) tasks → VSTM

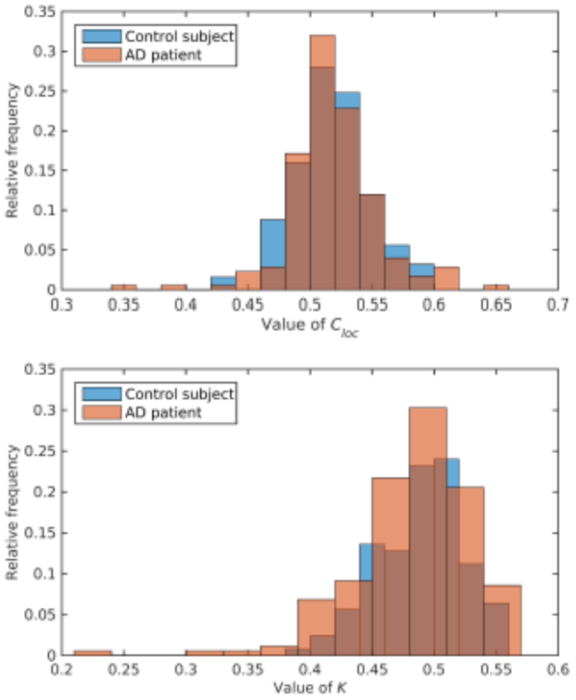
Pilot: Variability in EEG connectivity in AD

- Graph features computed from short-time connectivity matrices
  - Evaluation of the their distribution for each subject
- 1s resting-state EEGs from AD patients and controls
  - Distribution across trials of
    - Clustering coefficient (C_{loc}) / Average degree (K) / Efficiency (E)
  - Statistical moments
    - Mean / Variance / Skewness / Kurtosis
- Differences between groups and complementarity of features

Variability of resting state EEG connectivity

- Distributions with slightly different shape
  - Differences in moments other than the mean

- Additional support for the study of variability in EEG functional connectivity



AD patients' data have more frequent single values of the metrics (↑ kurtosis)

$\Longrightarrow$

Reduced repertoire of connectivity configurations in resting-state AD

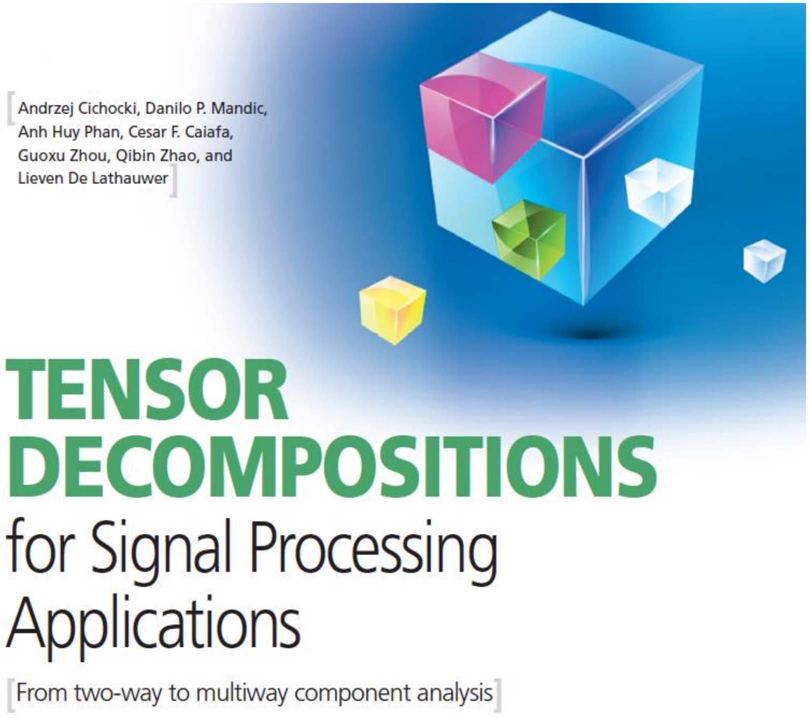
Escudero *et al.*, 2016, DOI: 10.1109/EMBC.2016.7591314

Vision

Challenges & Limitations

- EEG characteristics
  - Dynamic connectivity
  - Short recordings
  - Multi-frequency
- Methodological
  - Description of a single static topology
    - Multi-dimensional information
  - Samples over networks
    - What if we are not interested in the topology, but in data sampled over it? (Data over grids)
- Two recent techniques addressing some of these issues

Tensor factorisations



Journal of Neuroscience Methods 248 (2015) 59–69

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Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

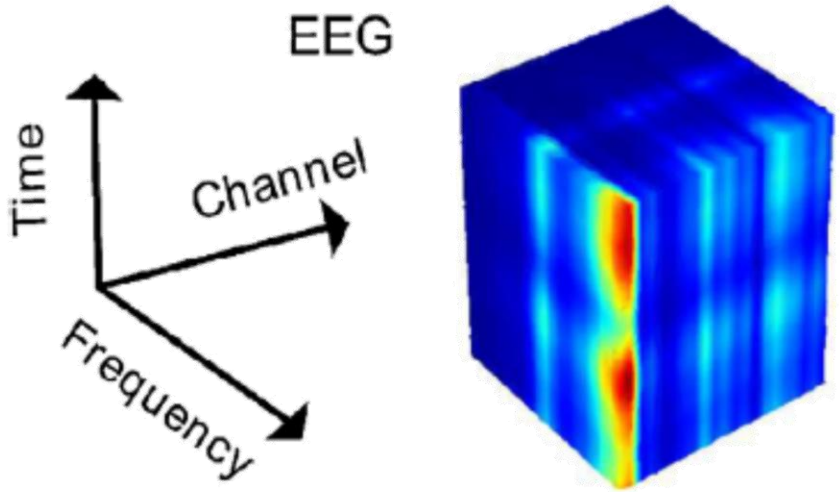
Computational neuroscience

Tensor decomposition of EEG signals: A brief review

Fengyu Cong[a,b,*], Qiu-Hua Lin[c], Li-Dan Kuang[c], Xiao-Feng Gong[c], Piia Astikainen[d], Tapani Ristaniemi[b]

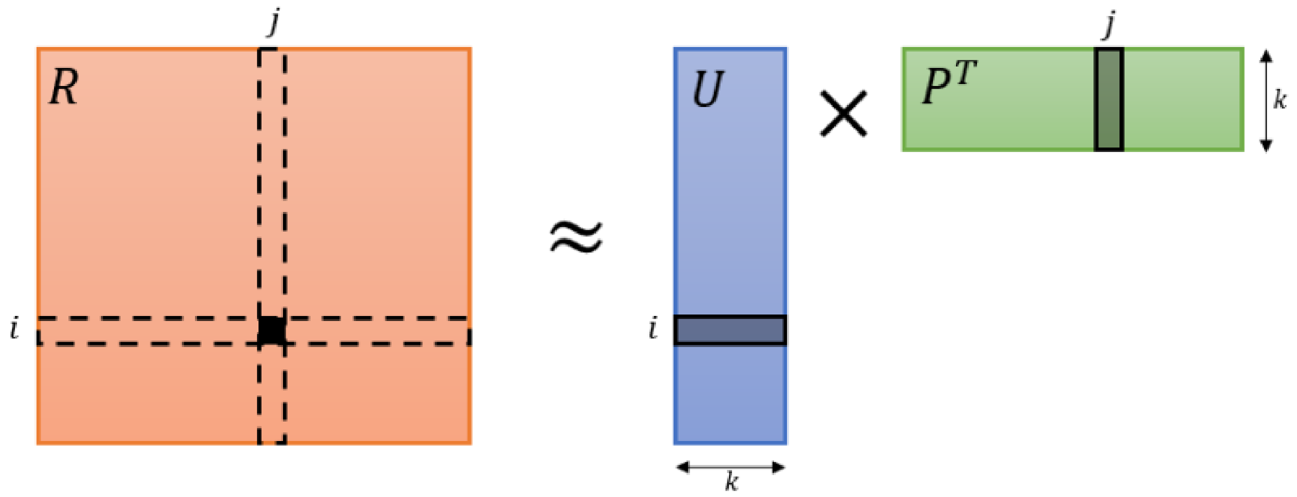
Motivation for tensor factorisations

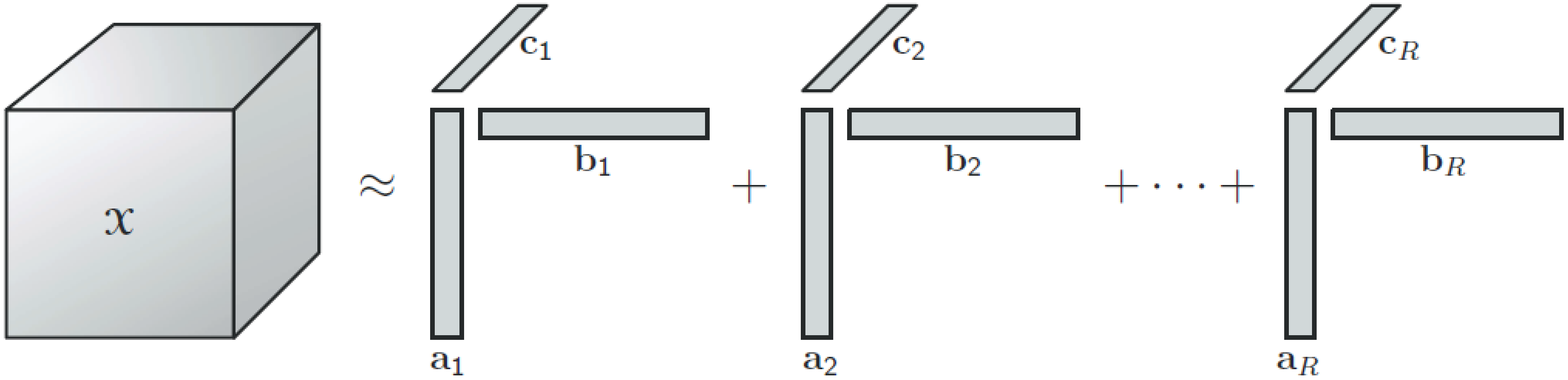
- Brain activity is highly multi-modal (multi-way)
  - Activity depends on more than one "domain"
    - Subjects, Time, Frequency, Voxels…
- Linkages in data → *n*-way arrays
  - Think higher-dimensional factor analysis!
    - Parsimonious and data-driven inspection of patterns that explain the relationships



Cong *et al.*, 2015, DOI: 10.1016/j.jneumeth.2015.03.018

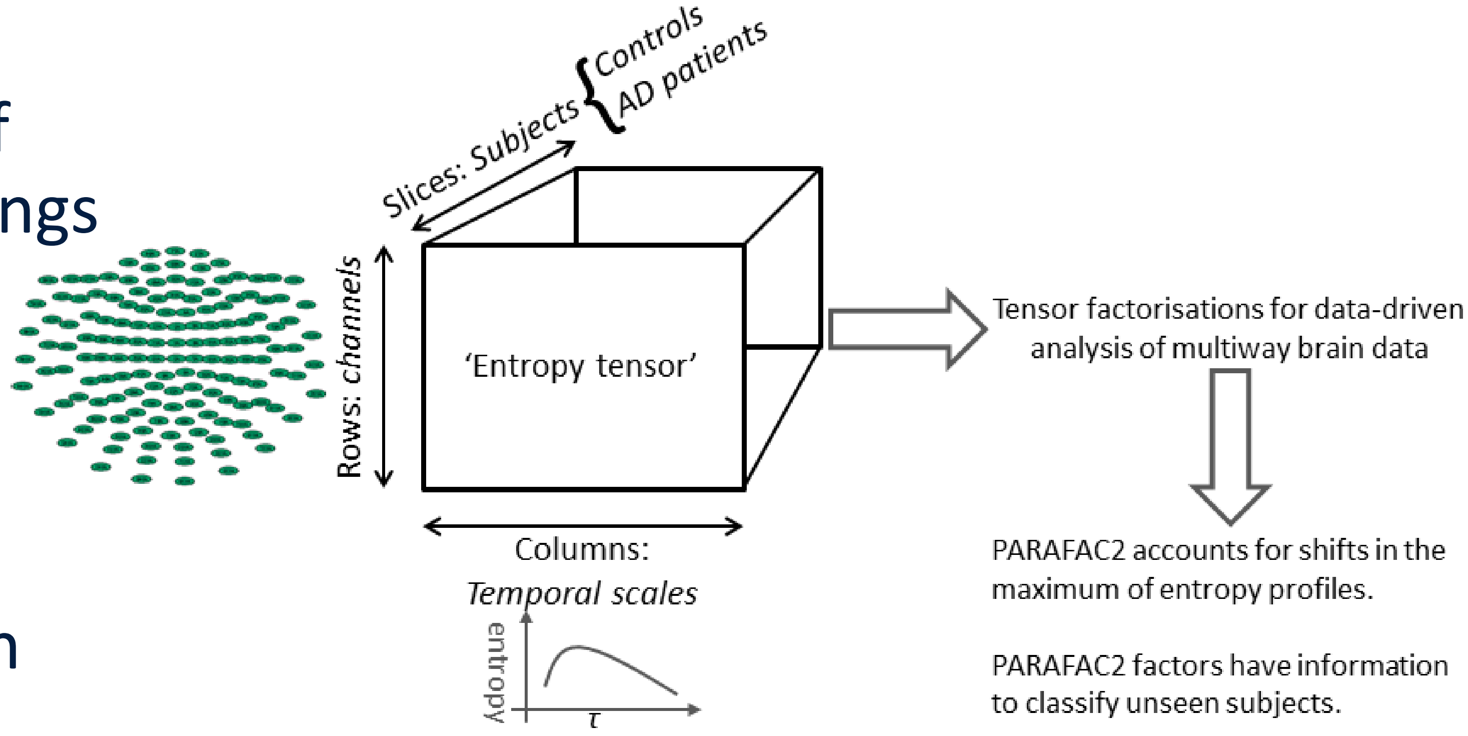
Tensor vs Matrix factorisation





Tensor factorisations for brain activity

- Inspection and modelling of electrophysiological recordings and their features
  - Extraction of sources (BSS)
  - Identification of patterns
- Further uses in classification



Escudero *et al.*, 2015, DOI: [10.1016/j.jneumeth.2015.03.018](https://doi.org/10.1016/j.jneumeth.2015.03.018)

Tensor factorisations of connectivity data

- Most work in power (amplitude) of EEG activity

- Many EEG functional connectivity based on the cross-spectrum
  - Complex-valued derived from Fourier Transform
  - Cross-source interference may degrade connectivity estimations

- Complex tensor factorisation to obtain scalp components described by frequency, spatial and trial profiles
  - PARAFAC2
  - Reduced cross-talk between components

Phase dependency estimations

- Phase-coupled activity in different areas
  - Systematic phase-delays over trials
- Challenges
  - Common reference & volume-conduction
  - Noise
  - Sample size bias

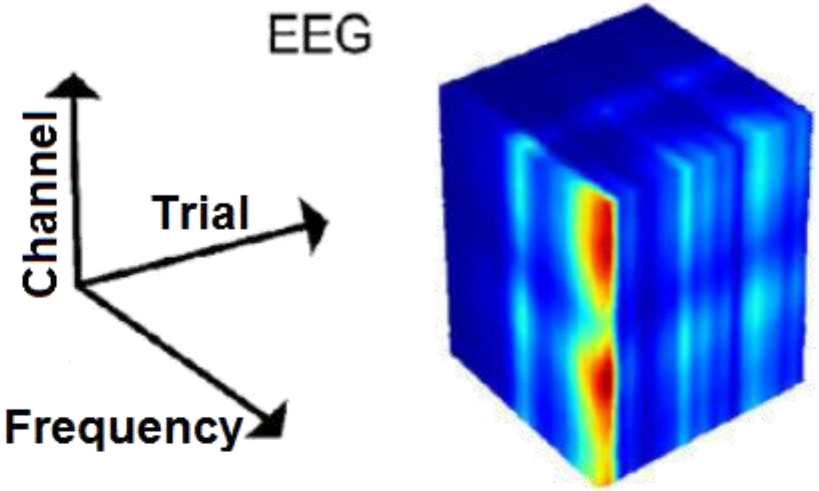
$$\mathbf{X}(t) = \mathbf{A}\mathbf{S}(t) = \sum_{i=1}^{m} \mathbf{a}_i s_i(t)$$

- Activity model

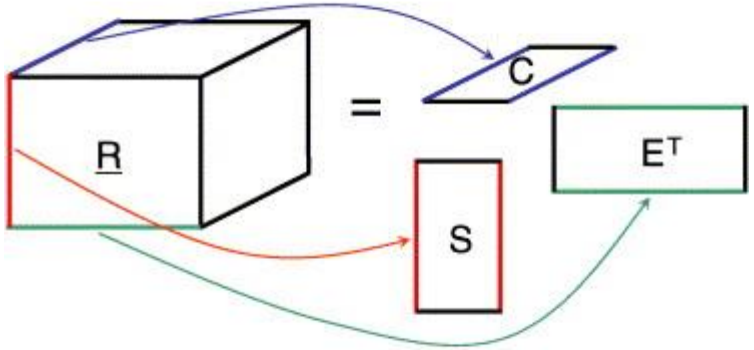
$$\begin{bmatrix} s_i(t) \\ s_j(t) \end{bmatrix} = \sum_{\tau=1}^{T} \begin{bmatrix} h_i(\tau) & h_{ij}(\tau) \\ h_{ji}(\tau) & h_j(\tau) \end{bmatrix} \begin{bmatrix} w_i(t-\tau) \\ w_j(t-\tau) \end{bmatrix}$$

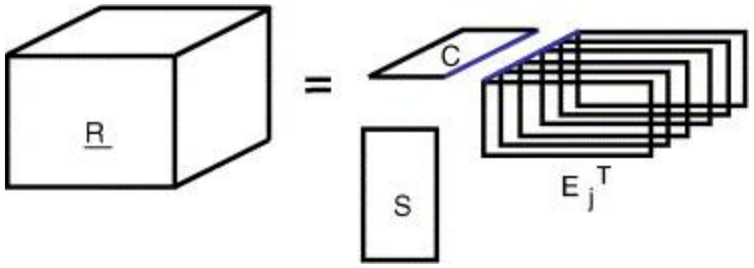
Spyrou *et al.*, 2017, In preparation

PARAFAC2 model development (I)



- Extend tensor factorisations to complex values
  - [Channel] x [Frequency] x [Trial]
- Estimation of EEG components
  - Unique profile per channel and trial
  - Limited variability in frequency
- EEG model in the complex domain that agrees with PARAFAC2

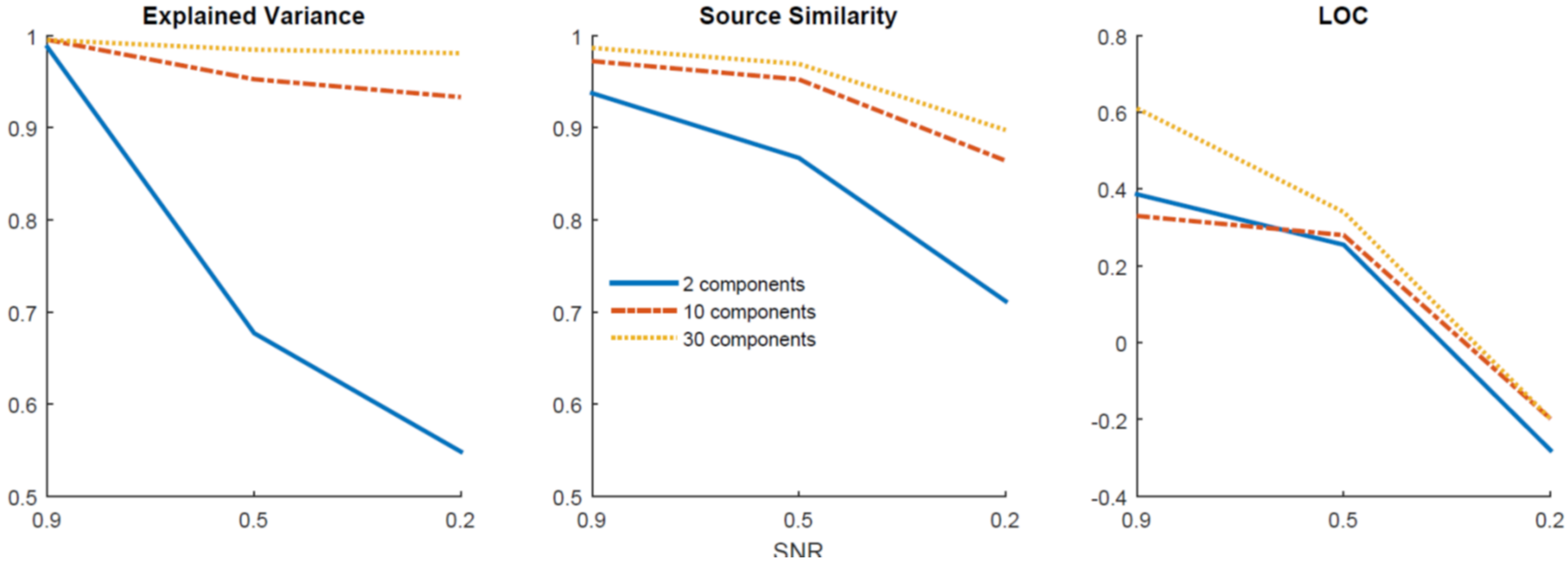




István *et al.*, 2006, DOI: 10.1016/j.chroma.2005.11.131

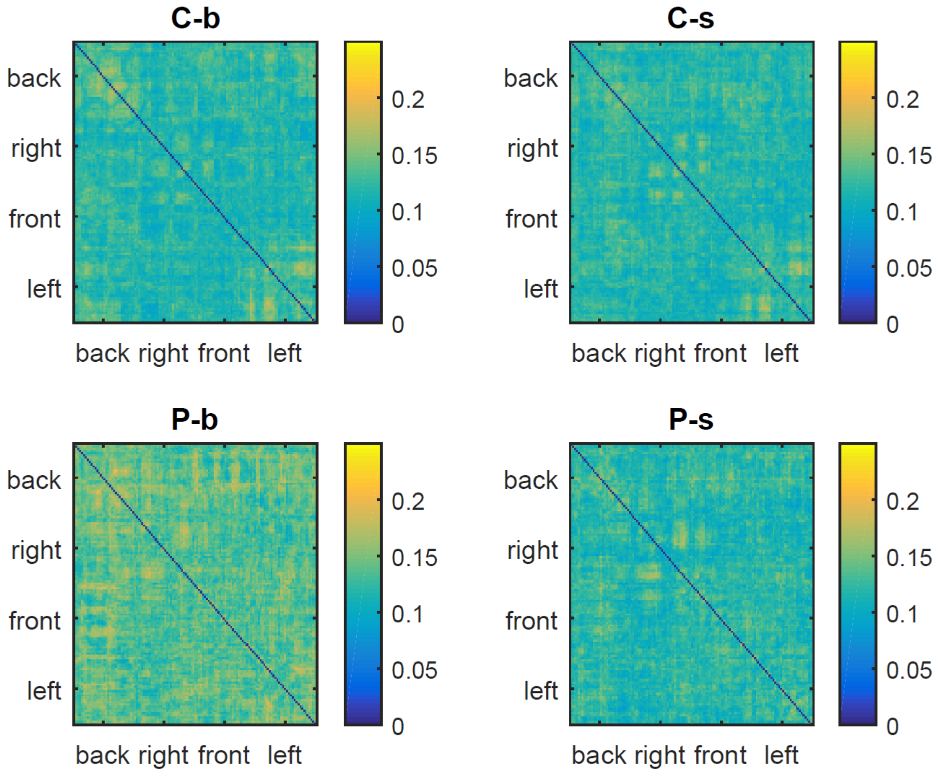
Results in benchmark

- Berlin Brain Connectivity Benchmark
  - Complex PARAFAC-2 algorithm able to decompose the underlying data into sources that reflect the true activity

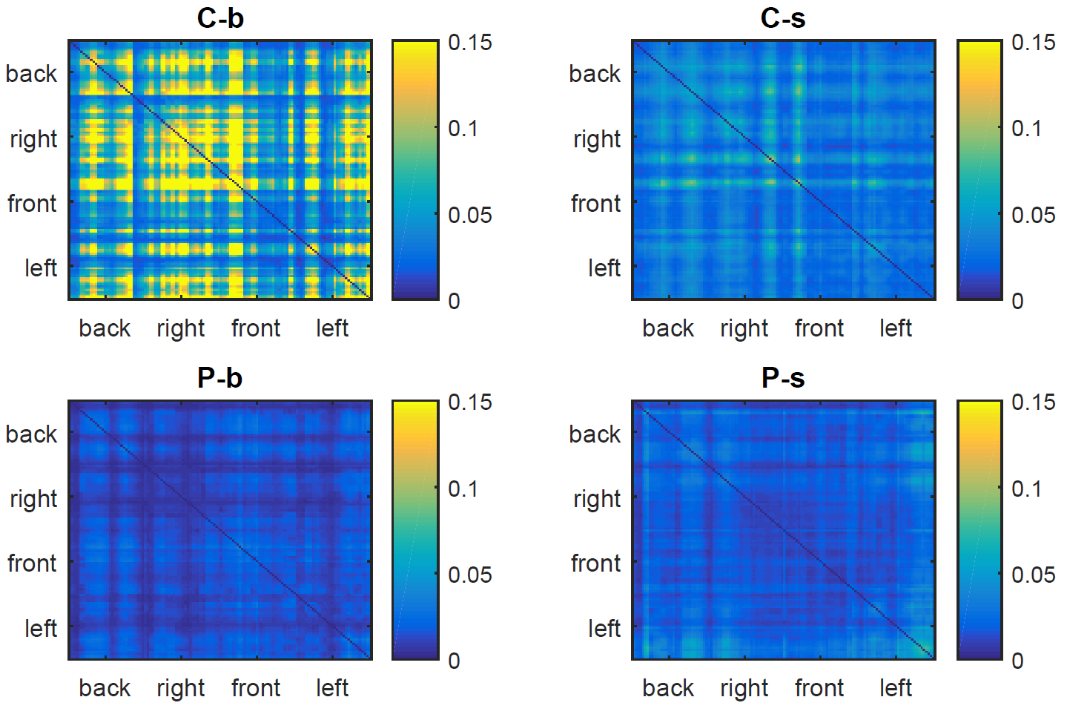


Connectivity in sporadic AD

Standard PLI



PARAFAC2-PLI

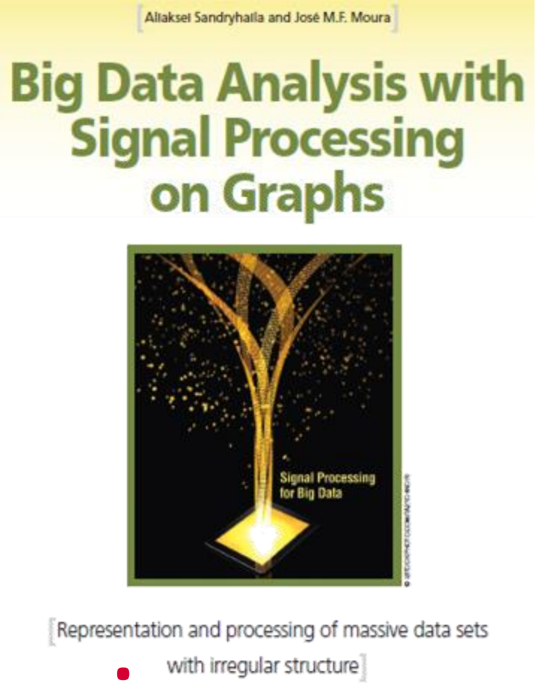


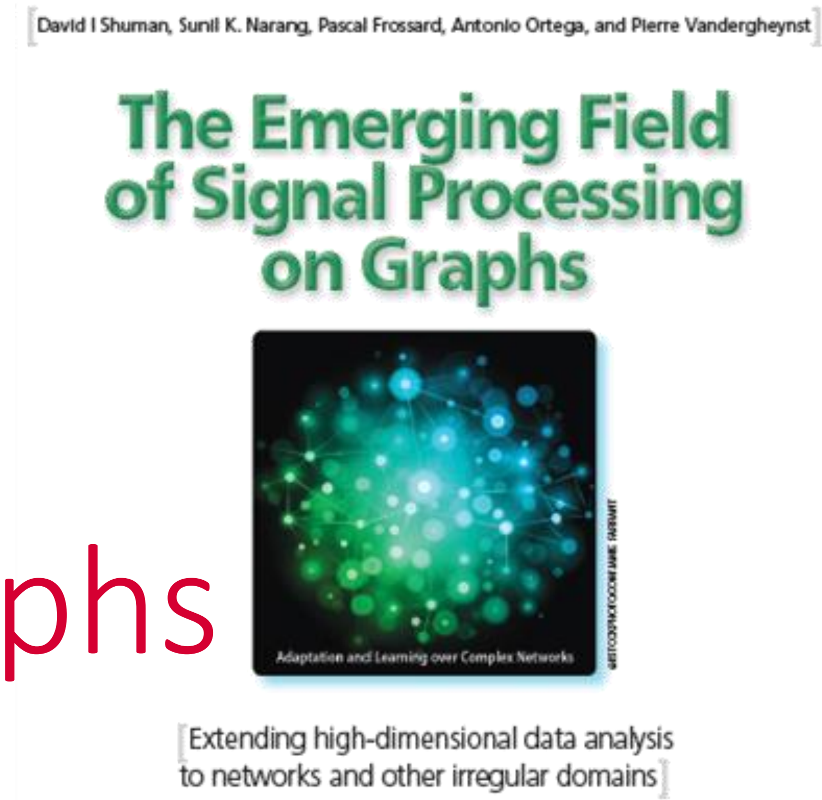
Comments on complex PARAFAC2

- Complex PARAFAC2 is suitable for EEG connectivity estimation
  - EEG data follow the PARAFAC2 model in the complex domain
  - Benchmark and EEG datasets

- Use of high-order methods suitable for extracting coupled activity

- Performing tensor factorisation in the complex domain allows for the connectivity information present in the data to be optimally exploited



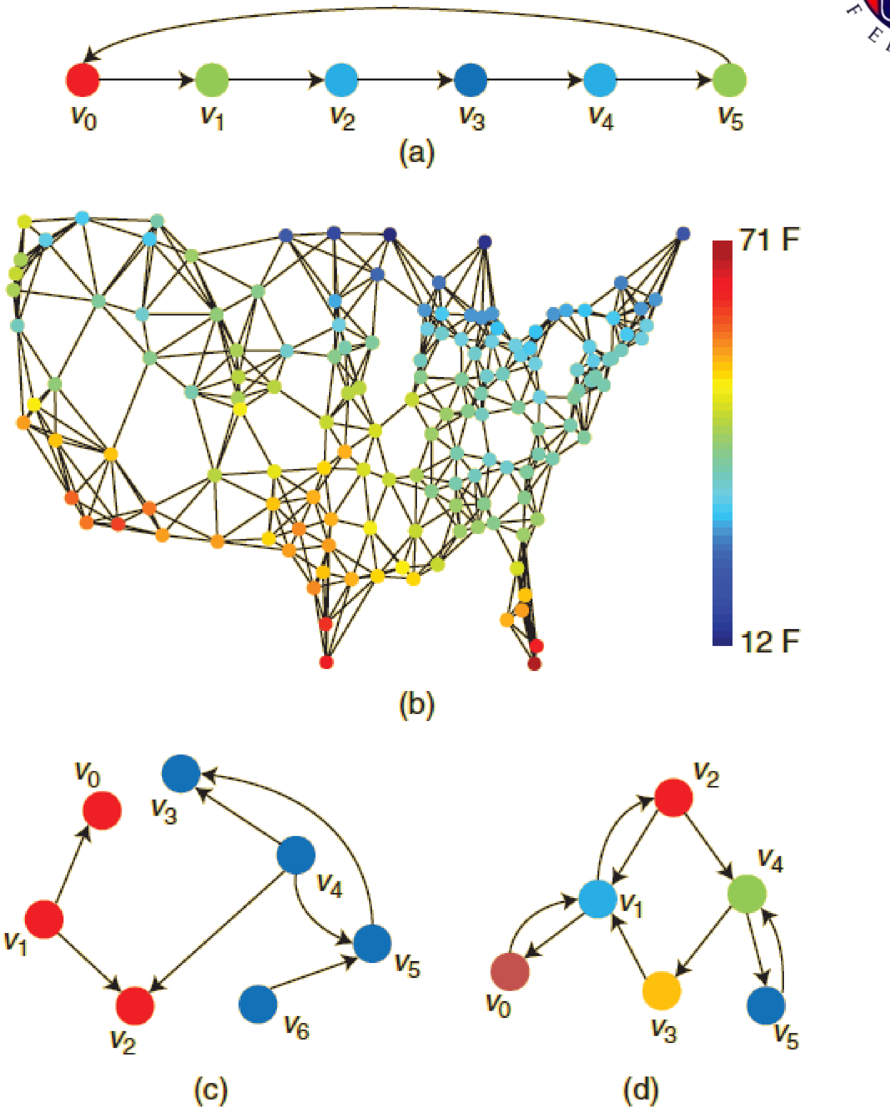


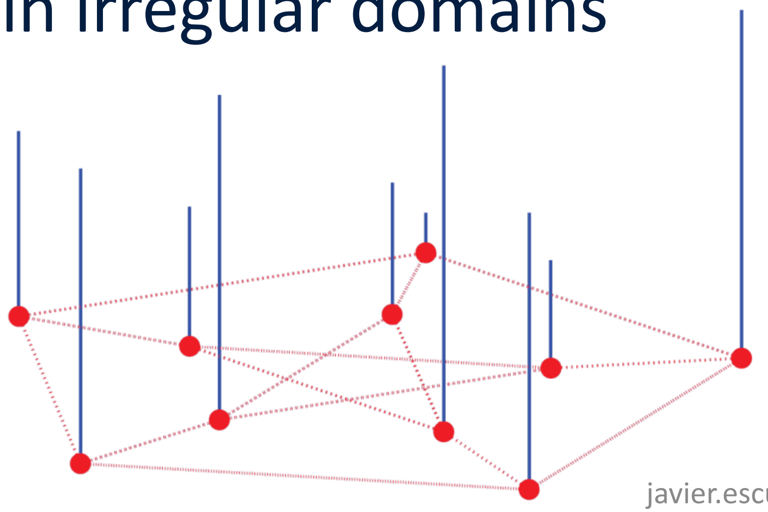
Signal processing on graphs

(Dynamics on networks)

Samples on graphs

- Interested in the network as “supporter” of recorded activity
  - Data reside on the nodes of the graph
- Weight of edge in the graph represents the similarity between its two nodes
- Signals in irregular domains

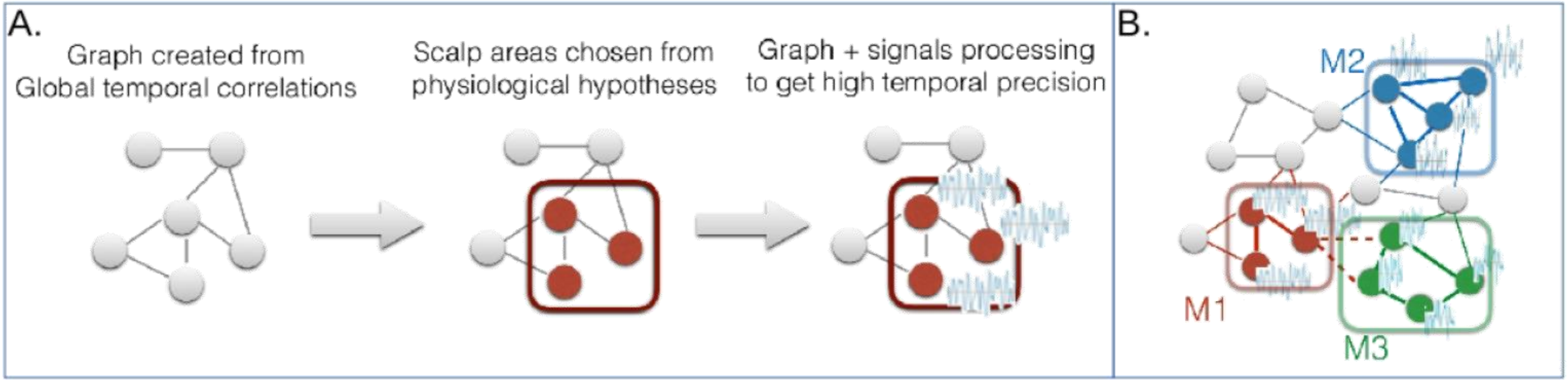




Shuman *et al.*, 2013, DOI: 10.1109/MSP.2012.2235192
Sandryhaila & Moura, 2014, DOI: 10.1109/MSP.2014.2329213

Framework for temporal signals over graphs

- Dynamic interactions in VSTMB task
- Each node of the graph corresponds to an EEG electrode
- Connection strength is the correlation of the whole time series

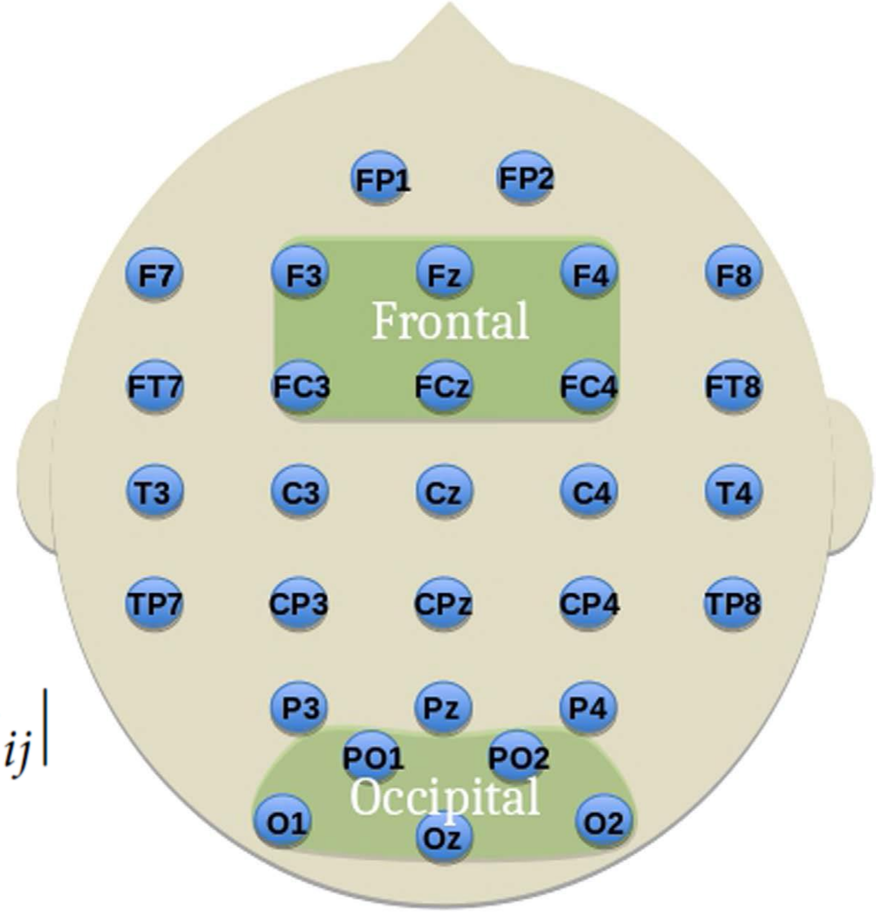


Smith *et al.*, 2017, DOI: [10.1038/srep42013](https://doi.org/10.1038/srep42013)

Framework for temporal analysis (I)

- Modular Dirichlet Energy (MDE)
  - Analysis of functional dependencies with high temporal precision
- Modules of the network defined by several channels over localised scalp regions
  - Reproducibility

$$\mathbf{W} = \begin{cases} w_{ij} & (i,j) \in \mathcal{E} \\ 0 & \text{otherwise} \end{cases} \qquad w_{\mathcal{V}_x} = \sum_{i \in \mathcal{V}_x} \sum_{j \in \mathcal{V}} |w_{ij}|$$



Framework for temporal analysis (II)

- Set-up
  - Weighted graph generated using coupling metrics
  - The time-series recorded at each EEG electrode is associated to the corresponding node
- Two levels of analysis
  - Connectivity information encodes stable signal dependencies over long windows
  - This acts as a filter for temporal analysis provided by the graph signals over a short window

Modular Dirichlet Energy

- MDE
  - Combination of Dirichlet energy (variability of time series) with the concept of modules from network science

$$w_{ij}(f_i - f_j)^2 \qquad MDE(\mathcal{G}_x) = \sum_{i \in \mathcal{V}_x} \sum_{j \in \mathcal{V}} w_{ij}(f_i - f_j)^2$$

- If coupling ↓ ➔ Magnitude of MDE is small: We cannot infer much from the signals
- If coupling ↑
  - w_{ij}>0 and difference is ↑ ➔ MDE is positive and large ➔ Likely discrepancy between the coupling over the long epoch and the signal behaviour at time *t*

Smith *et al.*, 2017, DOI: [10.1038/srep42013](https://doi.org/10.1038/srep42013)

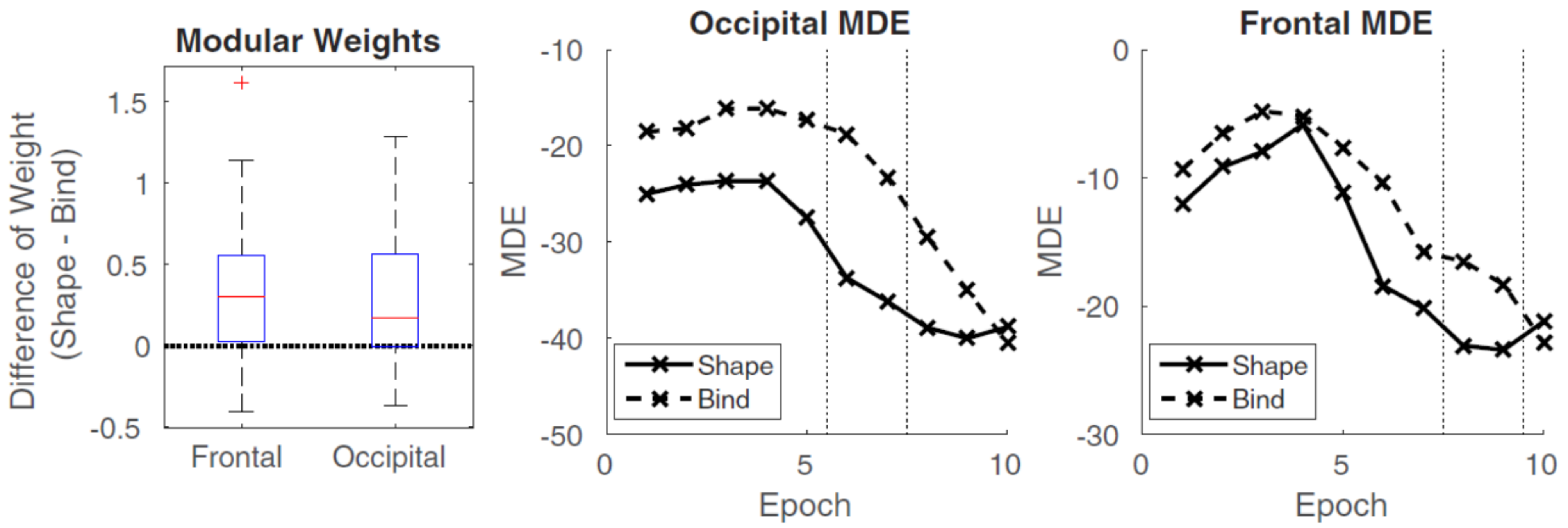
Interpretation in tasks

- w_{ij} is significantly larger in condition R than in condition S
  - In general $w_{ij}(R)(f_i(R) - f_j(R))^2 > w_{ij}(S)(f_i(S) - f_j(S))^2$
  - Most apparent where there is abnormal activity occurring in one of the conditions over the signal
  - Indicative of a 'driving effect' for the coupling of a point in time in which the connectivity combined with the signal amplitudes is particularly important

- If the driving effect occurs at a point where the MDE of one of the conditions undergoes a considerable change, we can infer that that condition shows a change in effect not noted in the other condition

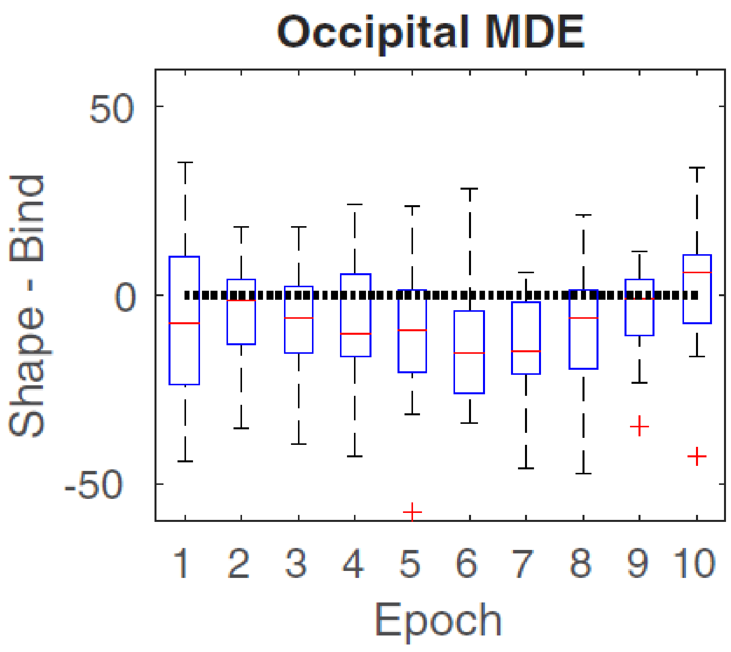
Results (I)

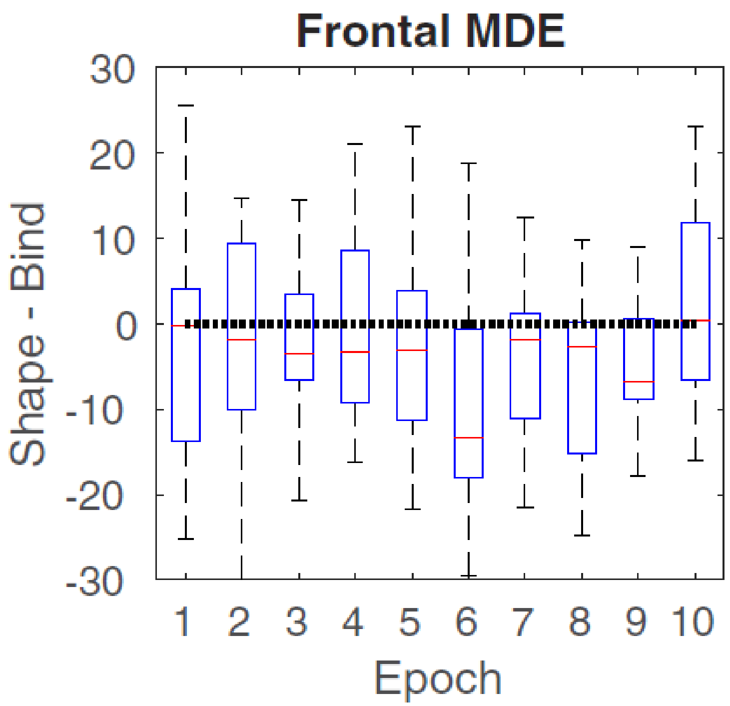
- Two-level hierarchical statistical test probing for differences between shape and binding

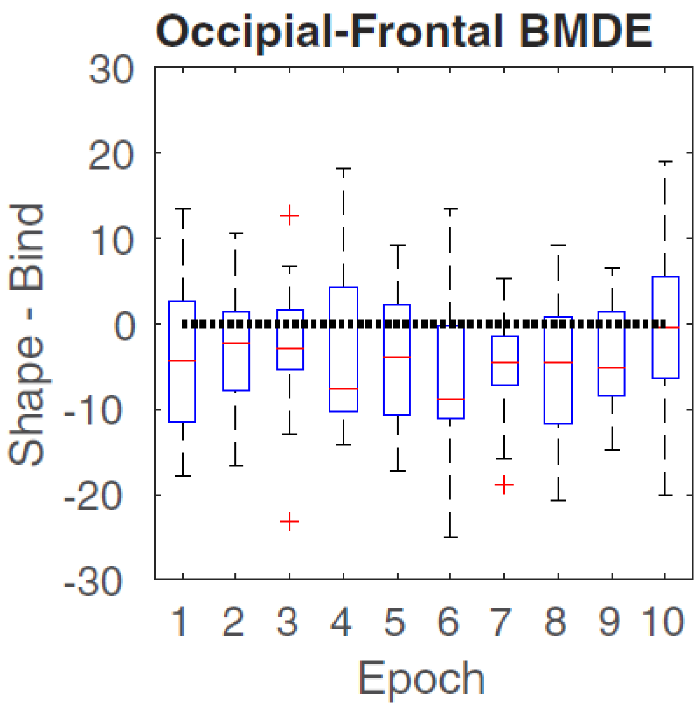


Smith *et al.*, 2017, DOI: 10.1038/srep42013

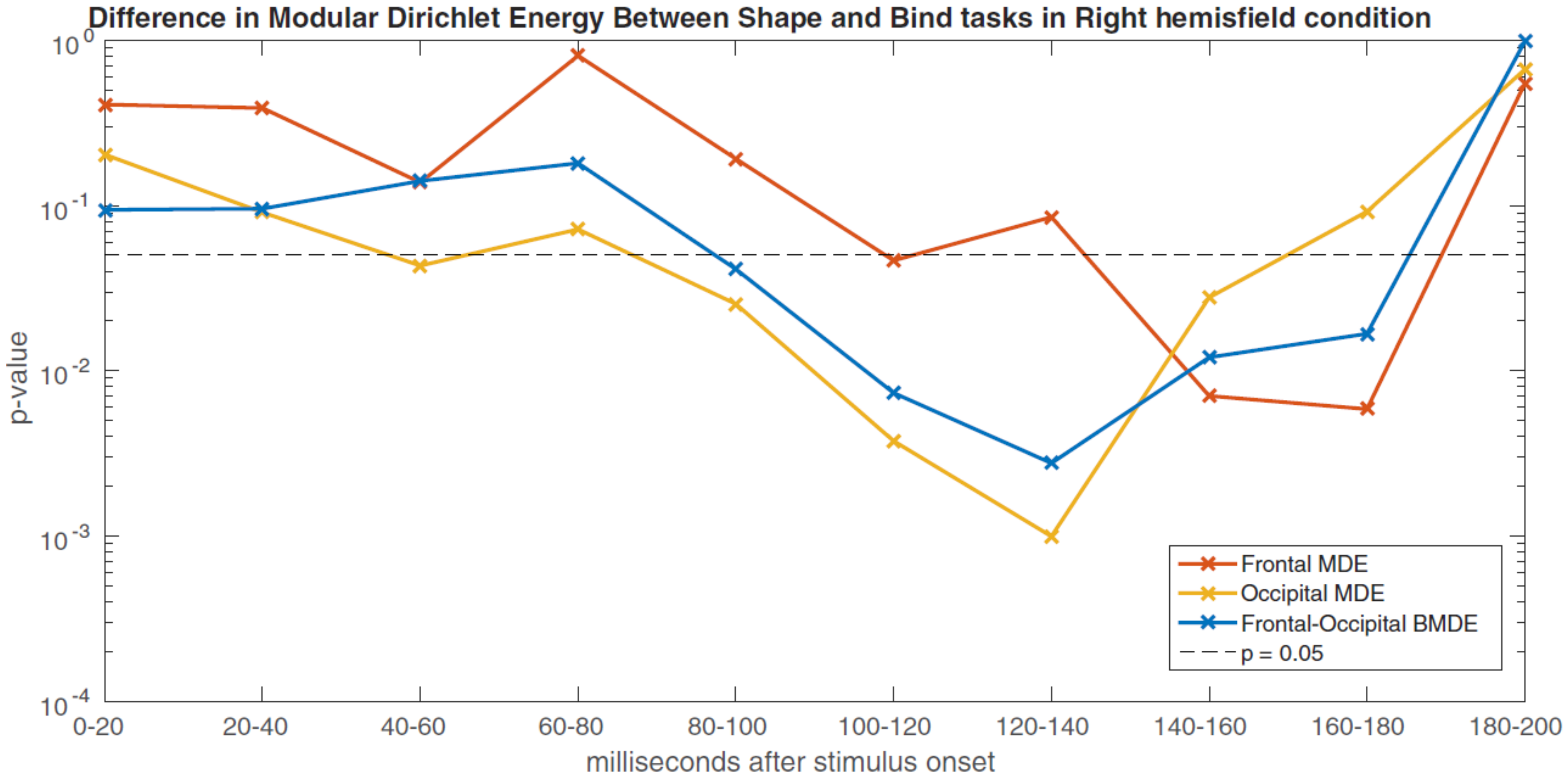
Results (II)


Occipital MDE
50
0
-50
Shape - Bind
1 2 3 4 5 6 7 8 9 10
Epoch


Frontal MDE
30
20
10
0
-10
-20
-30
Shape - Bind
1 2 3 4 5 6 7 8 9 10
Epoch


Occipial-Frontal BMDE
30
20
10
0
-10
-20
-30
Shape - Bind
1 2 3 4 5 6 7 8 9 10
Epoch

Results (III)



Difference in Modular Dirichlet Energy Between Shape and Bind tasks in Right hemisfield condition
p-value
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0-20
20-40
40-60
60-80
80-100
100-120
120-140
140-160
160-180
180-200
milliseconds after stimulus onset
Frontal MDE
Occipital MDE
Frontal-Occipital BMDE
p = 0.05

Comments on MDE

- Temporal activations agree with ERP and electrophysiological hypotheses

- MDE seeks to overcome the reduced reliability of connectivity information obtained from short windows (few temporal samples)
  - Suitable for rapid temporal dynamics

- The activity is encoded in the graph signal rather than in the edge weights of a time-varying graph

Conclusions

Conclusions

- Much information yet to be extracted from EEG activity
- Methodological developments informed by electrophysiology
- Building on multivariate, higher-order relationships in the data
- Extraction of transient, complex patterns with tools based on emerging signal processing fields
  - Inspection of potentially clinically relevant features

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1-day meeting

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Tensor Theory and Applications Meeting

Location: Sanderson Building, King's Buildings, EH9 3JL

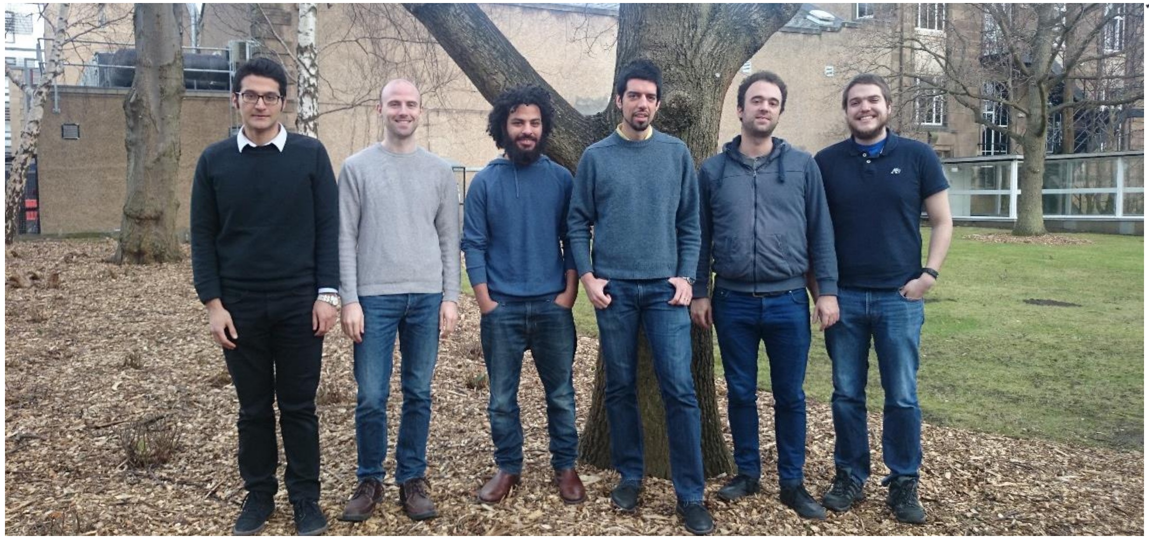
Date: Thursday, March 30, 2017 - 09:30 to 17:30

The goal of the meeting is to bring together researchers in the theory and application of tensor based methods. The scope is to disseminate the current methodology in tensor analysis and the communication of algorithms, technologies, practical issues and applications

Event Contact Name: Dr Javier Escudero

Event Contact Email: javier.escudero@ed.ac.uk

Thank you!



- The team!
  - Special mention to Loukianos Spyrou and Keith Smith
- Collaborators in AD
  - Prof John Starr
  - Dr Mario Parra
- Tensors, Univ. Copenhagen
  - Prof Rasmus Bro
  - Dr Evrim Acar
- Graph signal processing, EPFL
  - Prof Pierre Vandergheynst

Heriot Watt University Neurophysiology Lab

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