Resting state functional connectivity in epilepsy

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Multi FunkIm
Multimodal Functional Imaging Laboratory

neuro

BME

Outline

- Multimodal exploration of the epileptic network
- Group level analysis of functional connectivity in epilepsy
- Patient-specific functional connectivity patterns

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- **Multimodal exploration of the epileptic network**
- Group level analysis of functional connectivity in epilepsy
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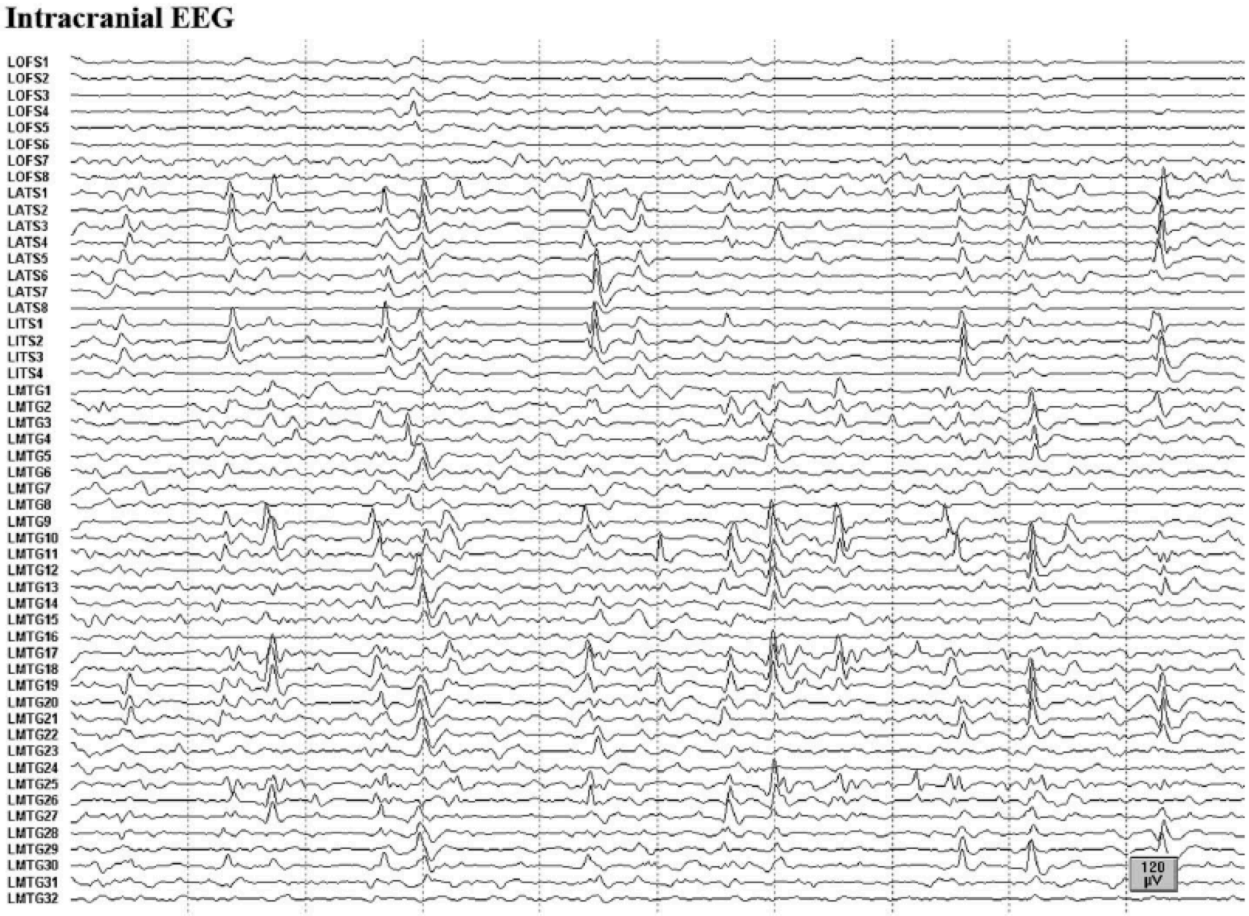
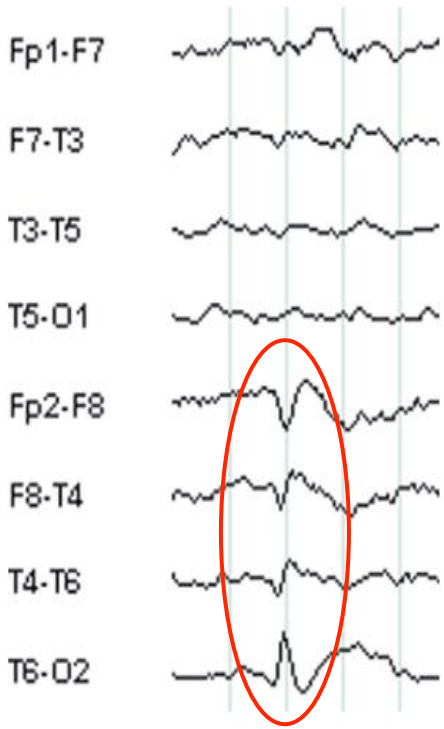
Spatially extended generators of epileptic discharges



Tao et al Clin Neurophys 2007

Clinical objective: Localizing the generators of epileptic activity

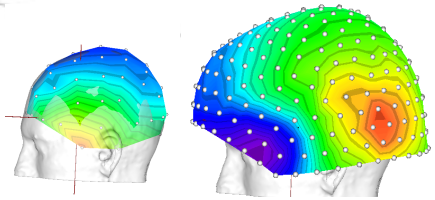


EEG interictal spike

- As opposed to epileptic seizures, **interictal epileptic spikes** are spontaneous activity generated by the brain without any clinical sign
  Multimodal exploration is feasible
- **EEG is required to detect spikes:**
  Simultaneous acquisition
  (EEG/fMRI, EEG/MEG, EEG/NIRS)
- Intra-cerebral EEG recordings showed that interictal spike generators are **rarely focal** *(Merlet I. et al. Clin. Neurophys. 1999)*
- A minimum brain activated area of **6 cm²** is needed to generate a spike on the scalp *(Ebersole J. Clin. Neurophys. 1997)*, spike generators may also be quite more extended than 6 cm² *(Tao et al Clin Neurophys 2007)*
- A minimum brain activated area of **3-4 cm²** is needed to generate spikes on MEG *(Oishi et al Epilepsia 2002, Huiskamp et al Brain Topo 2002)*

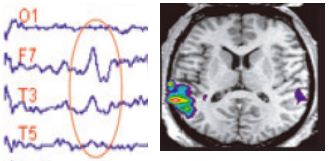
Multimodal integration of functional modalities exploring electrophysiology and hemodynamic processes during epileptic discharges

1. Simultaneous EEG / MEG



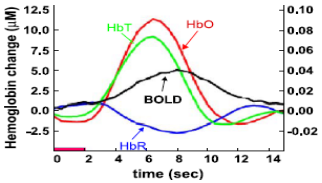
Detailed description of electrophysiology (electric vs magnetic)
Spatial resolution: scalp measurements
Source localization: inverse problem
Temporal resolution: 1 ms

2. Simultaneous EEG / fMRI



Hemodynamic correlates (BOLD) of EEG activity, within the whole brain volume
Spatial resolution: 3 mm
Temporal resolution: 1s
Origin of the BOLD signal:
-deoxy-hemoglobin (HbR): paramagnetic
-local variations of blood flow and volume

3. Simultaneous EEG / NIRS



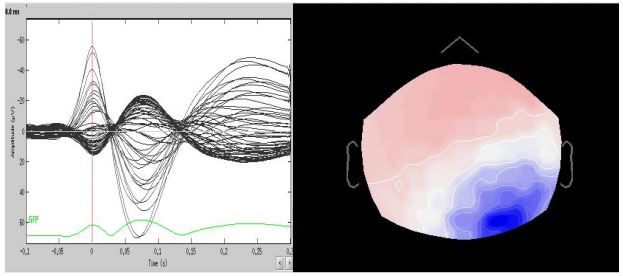
Local quantifications of variations in deoxy-hemoglobin (HbR) and oxy-hemoglobin (HbO) concentrations at the time of EEG interictal spikes
Spatial resolution: scalp measurements (depth = 1 cm of cortex)
Tomographic reconstruction: inverse problem
Temporal resolution : 1 ms

Source localization of spatially extended generators of of epileptic spikes measured with EEG/MEG

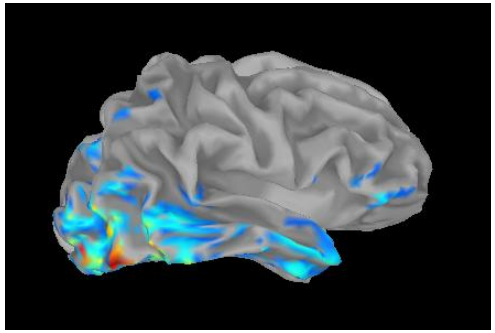
Source localization method dedicated to analyze epileptic activity

Maximum Entropy on the Mean (MEM): Chowdhury et al, PloS One 2013

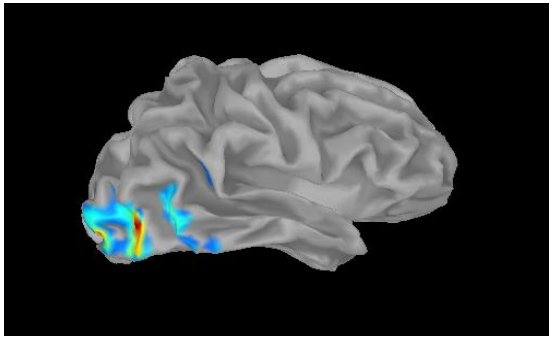
EEG spike



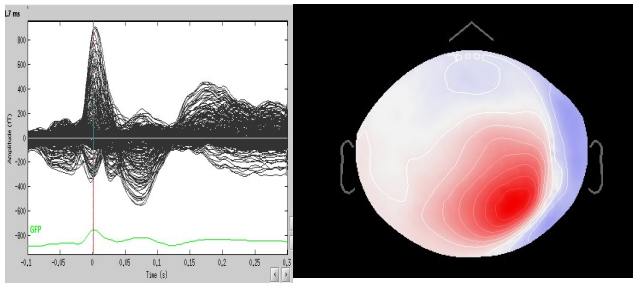
MNE



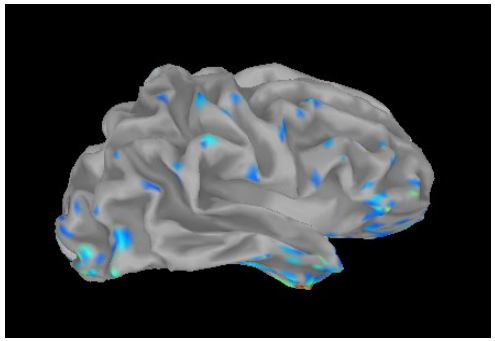
MEM



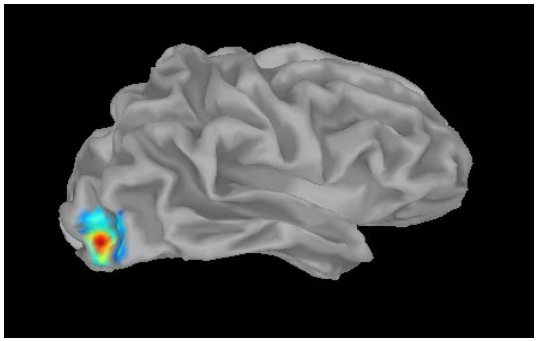
MEG spike



MNE



MEM



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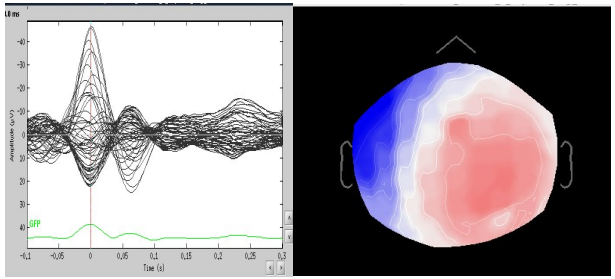

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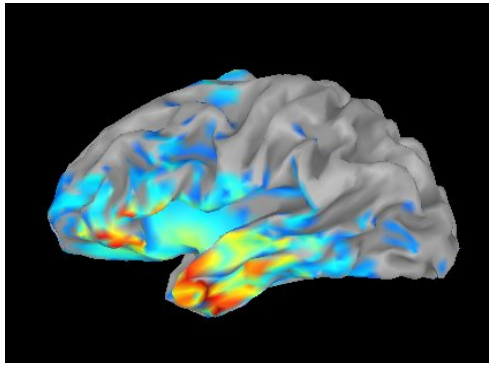
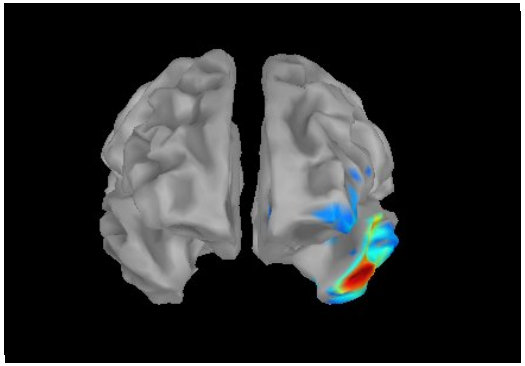
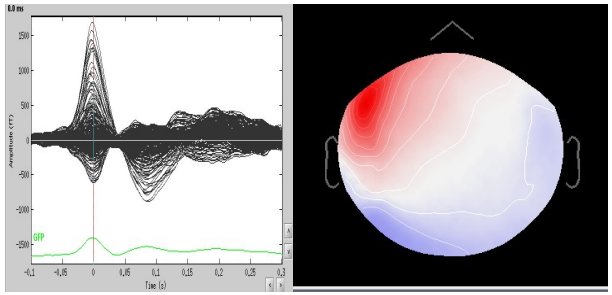


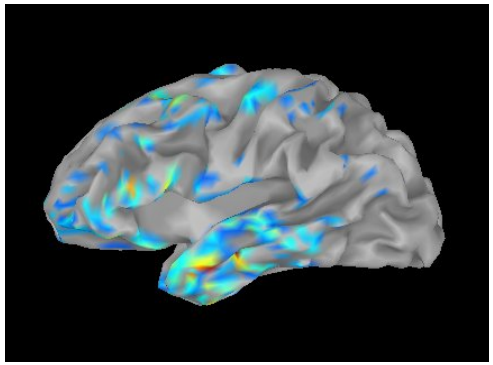
MEM



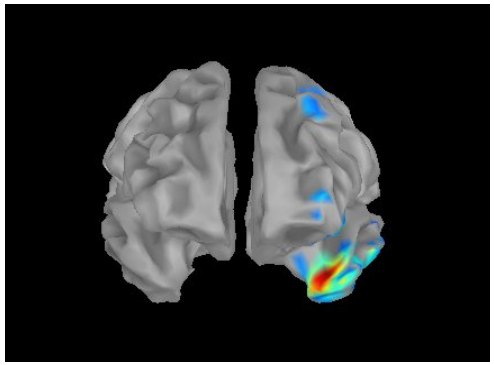
MEG spike



MNE



MEM



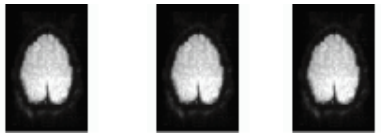
Simultaneous EEG/fMRI: acquisition

fMRI acquisition

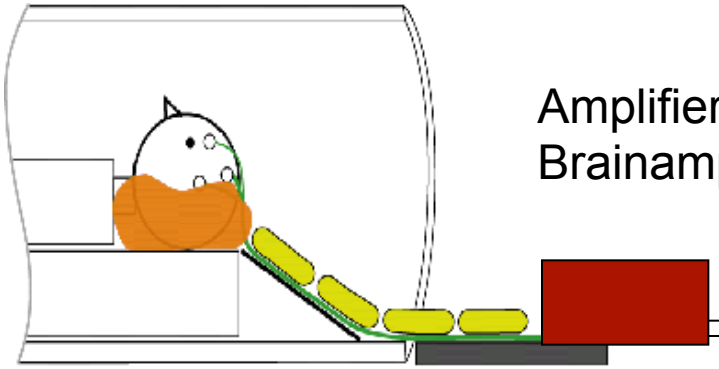
1 run = 120 EPI volumes

Matrix = 25x64x64, voxel = 5mm

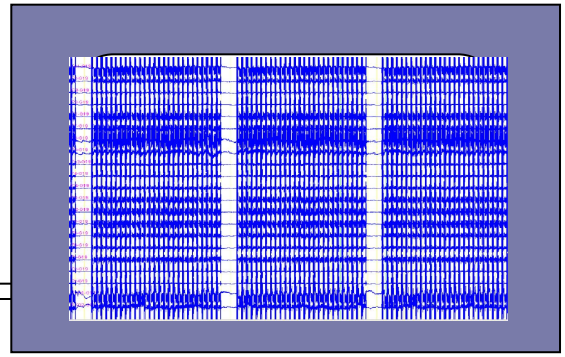
TR = 3s TE = 50 ms



21 Ag/AgCl MR compatible electrodes in the MRI (1.5T, Sonata, Siemens)



Amplifier
Brainamp 5kHz

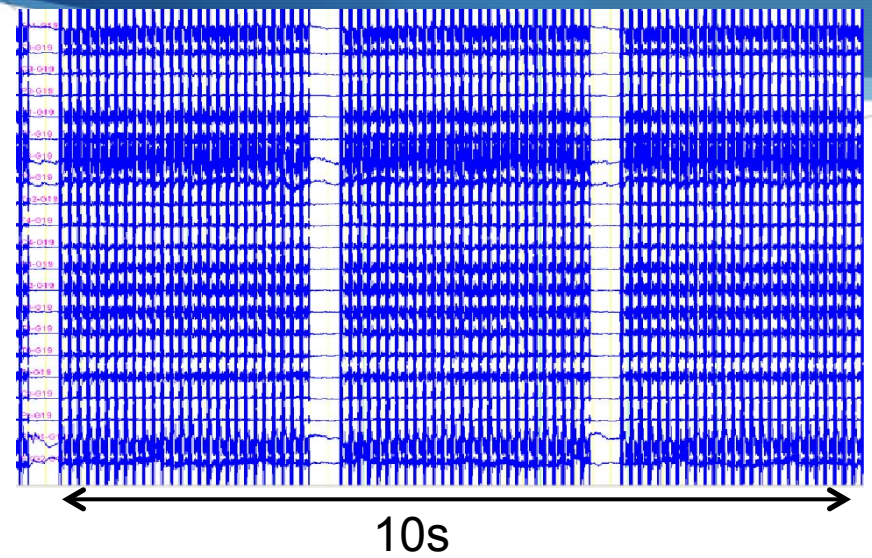


Optic fiber

EEG recording

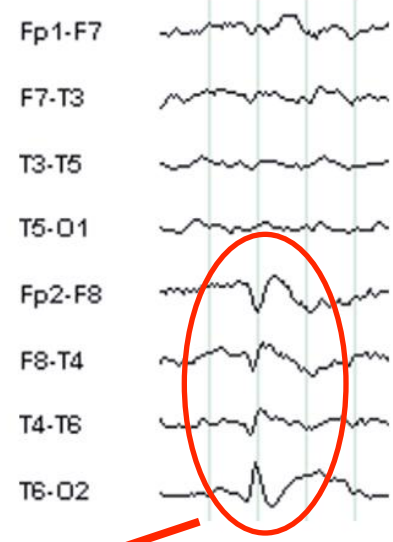
2 hours of simultaneous recording (5-12 runs/session)

Simultaneous EEG/fMRI: data analysis



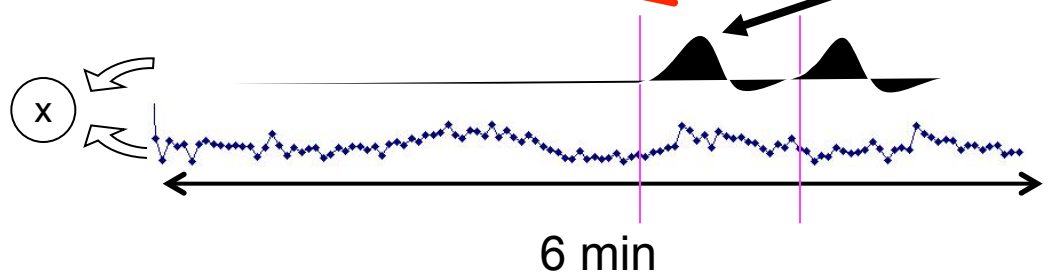
Artifact removal

EEG after filtering
manual spike detection

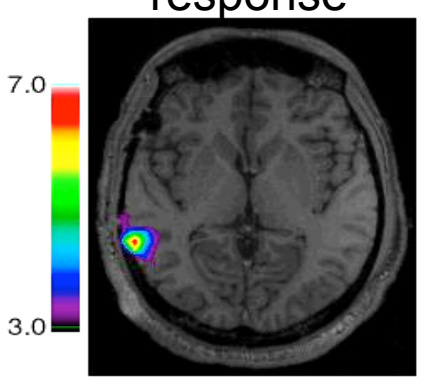


HRF Model

Generalized Linear Model:
Event-related design



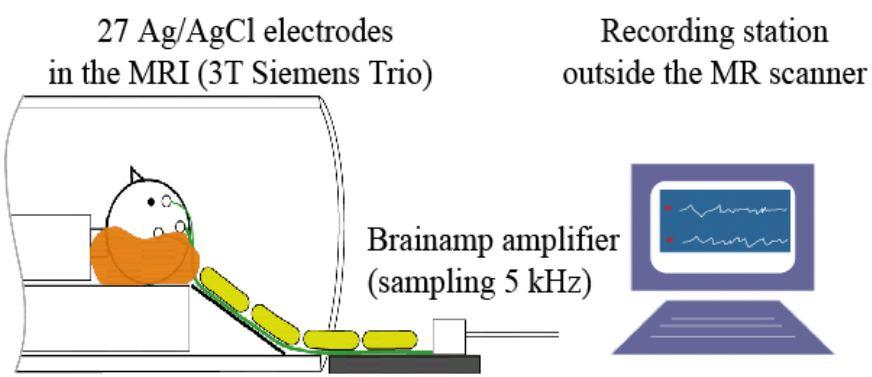
t-map of the fMRI response



Multimodal analysis of interictal epileptic activity

Simultaneous EEG/fMRI

Hemodynamic response
associated to epileptic discharges
(time res: 1s, space res: 2mm)



Simultaneous EEG/MEG

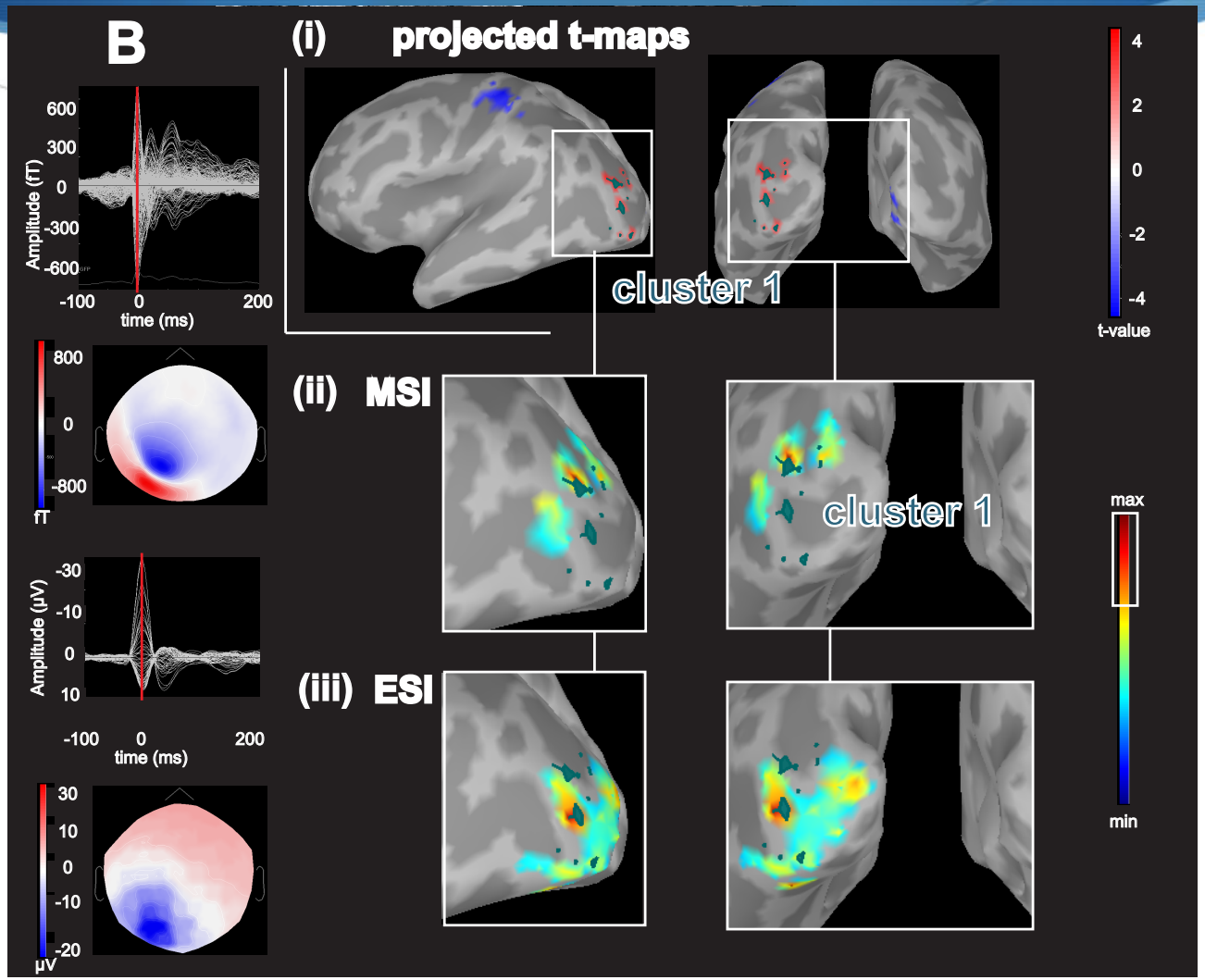
Scalp electric and magnetic activity
generated by epileptic discharges
(time res: 1ms, space res: 1cm)

CTF System:

275 MEG sensors
+
56 EEG electrodes

Common anatomical support: 3D cortical surface from anatomical MRI
Common functional support: EEG in both simultaneous acquisitions

Multimodal concordance: EEG sources, MEG sources and fMRI BOLD response to spikes



fMRI

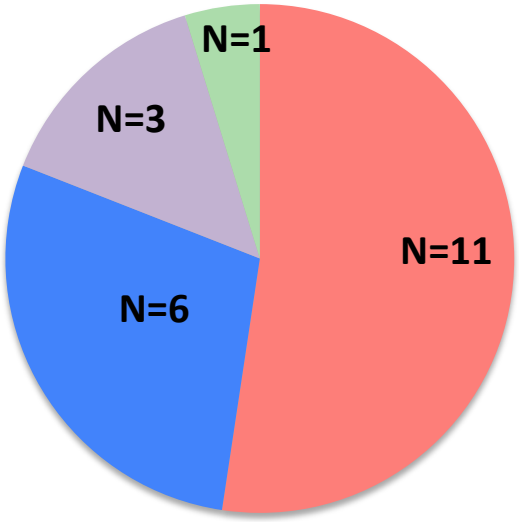
MEG

EEG

Heers et al, submitted

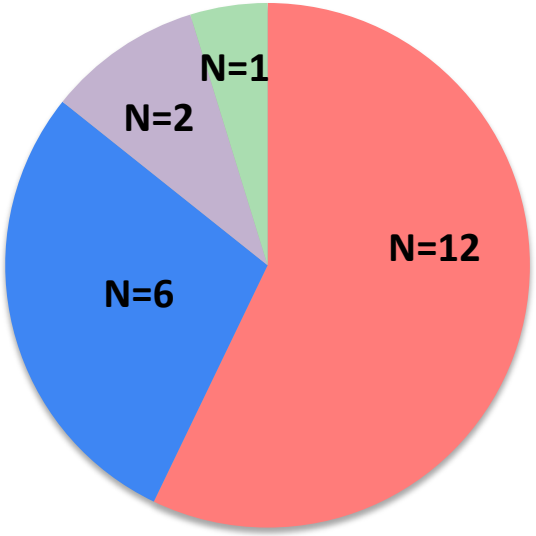
Multimodal concordance between BOLD, EEG source imaging, and MEG source imaging on 21 patients

BOLD vs EEG sources



- activation + ESI
- deactivation + ESI
- activation + MSI, but not ESI
- none

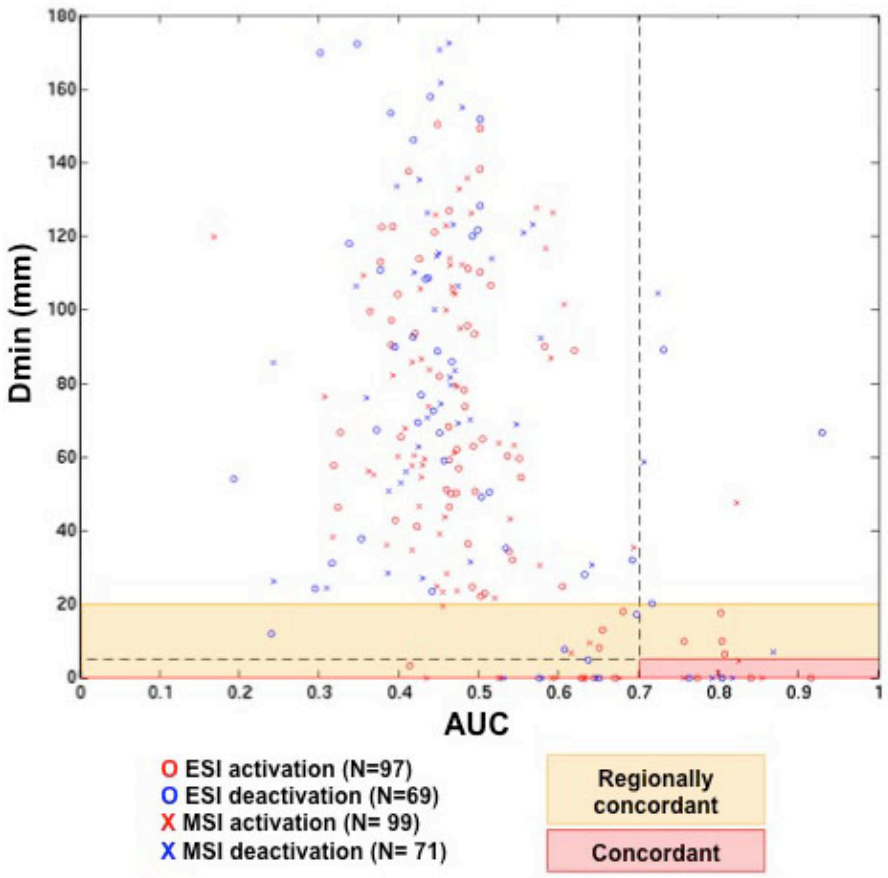
BOLD vs MEG sources



- activation + MSI
- deactivation + MSI
- activation + ESI, but not MSI
- none

N=21

Comparison between EEG source localization, MEG source localization and BOLD response



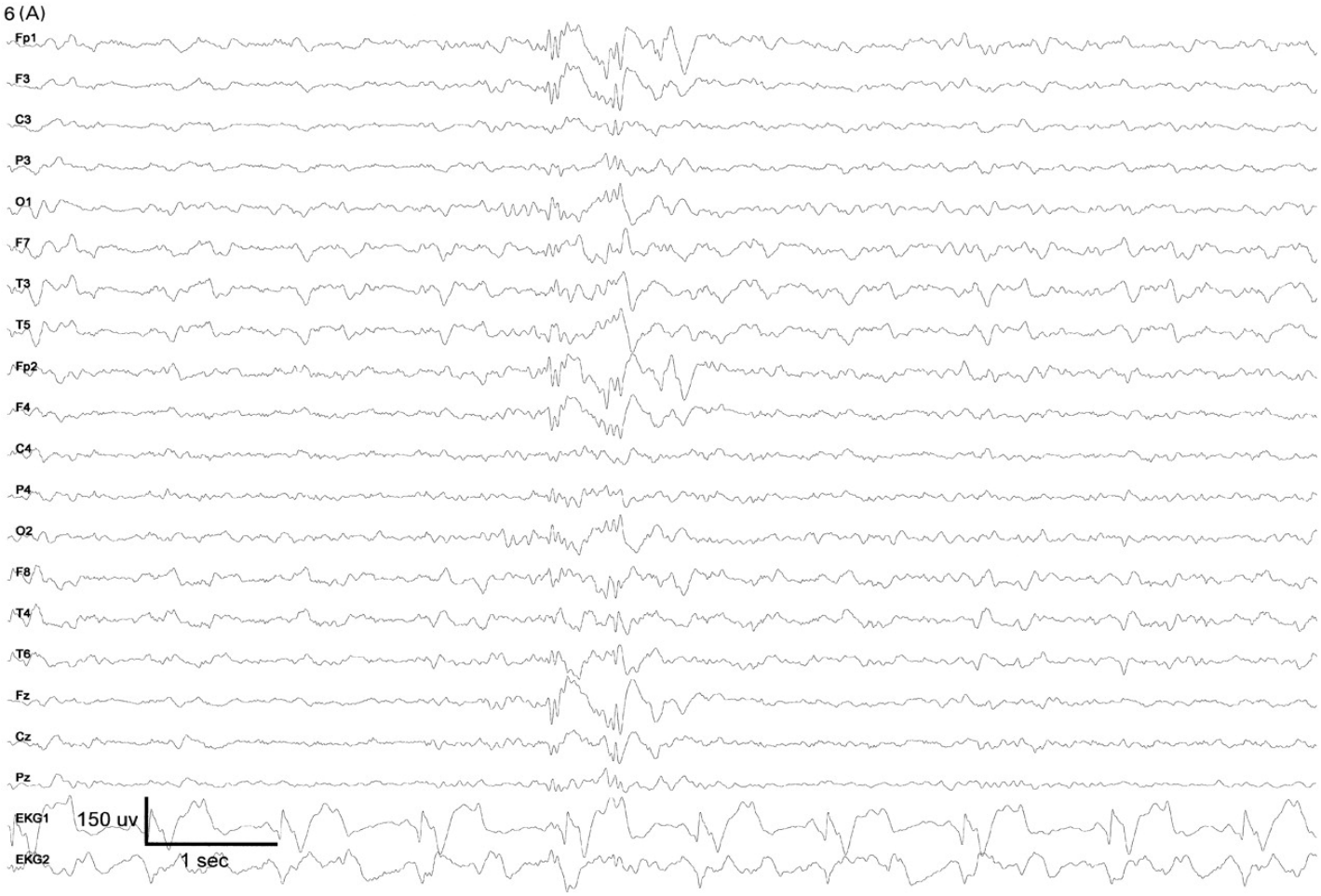
Distance between BOLD clusters and EEG/MEG sources as a function of the spatial overlap between BOLD and sources

For each patient, the most concordant cluster was the one showing the largest t-value

Inter-individual group analysis in epilepsy

- The majority of epilepsy studies in functional neuroimaging should be patient specific
- Only in specific conditions, epilepsy patterns are reproducible within a patient group
  - Idiopathic Generalized Epilepsy (IGE)
  - Temporal Lobe Epilepsy (TLE)

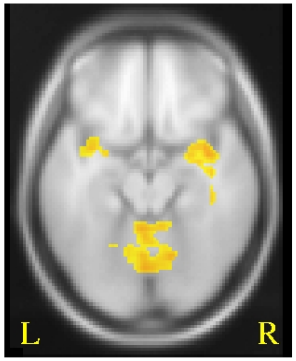
BOLD response to generalized spike and wave discharges: Group analysis of 15 patients with Idiopathic Generalized Epilepsy (IGE)



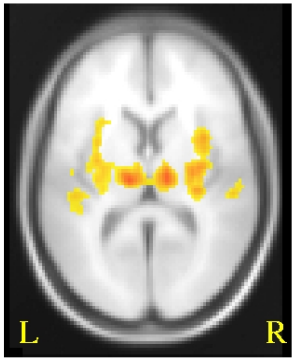
Aghakhani Y et al. Brain 2004;127:1127-1144

Gotman J., Grova C. et al. PNAS 2005

BOLD response to generalized spike and wave discharges: Group analysis of 15 patients with Idiopathic Generalized Epilepsy



A



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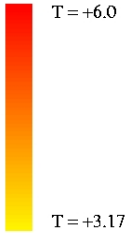

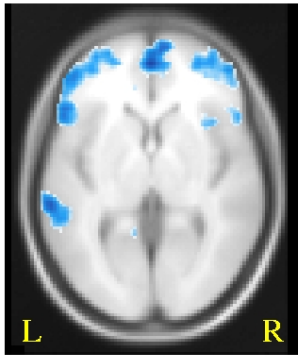

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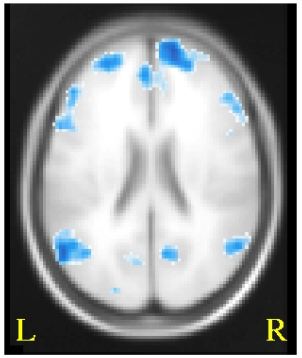

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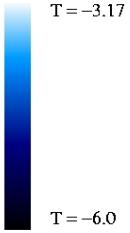
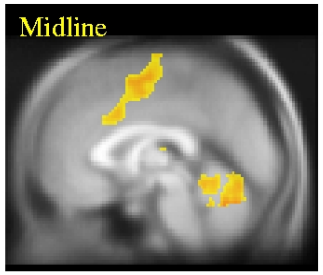
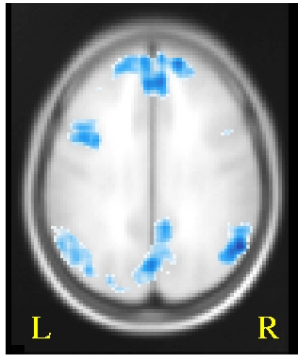




C



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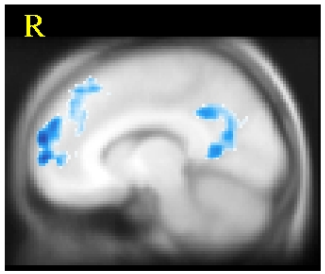
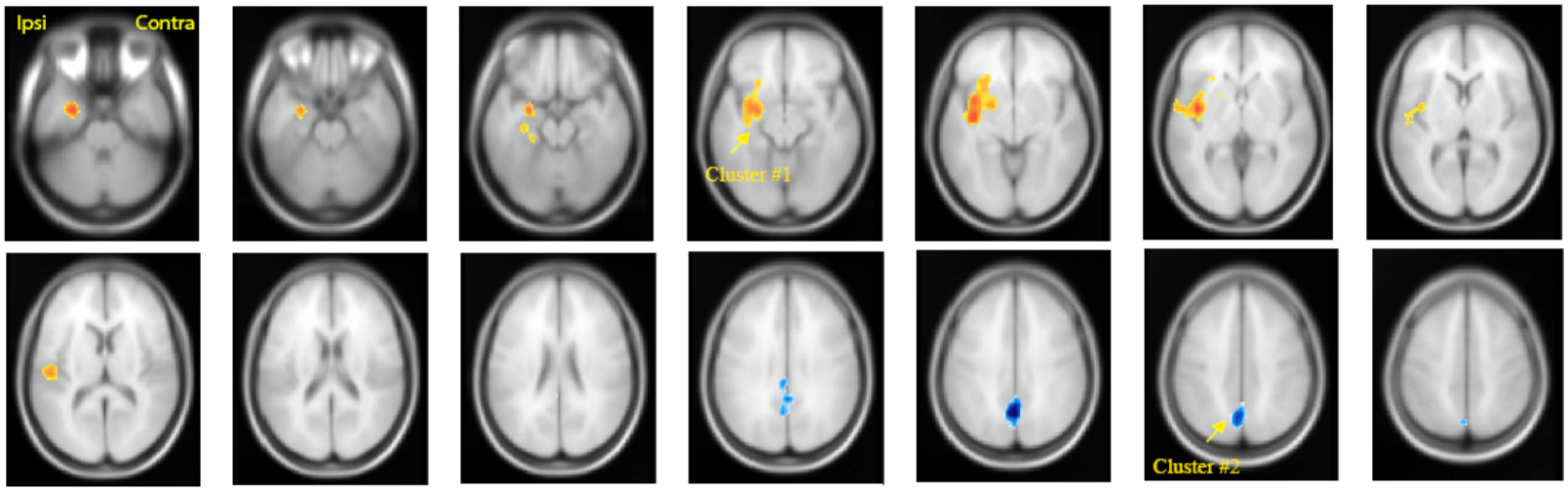


D

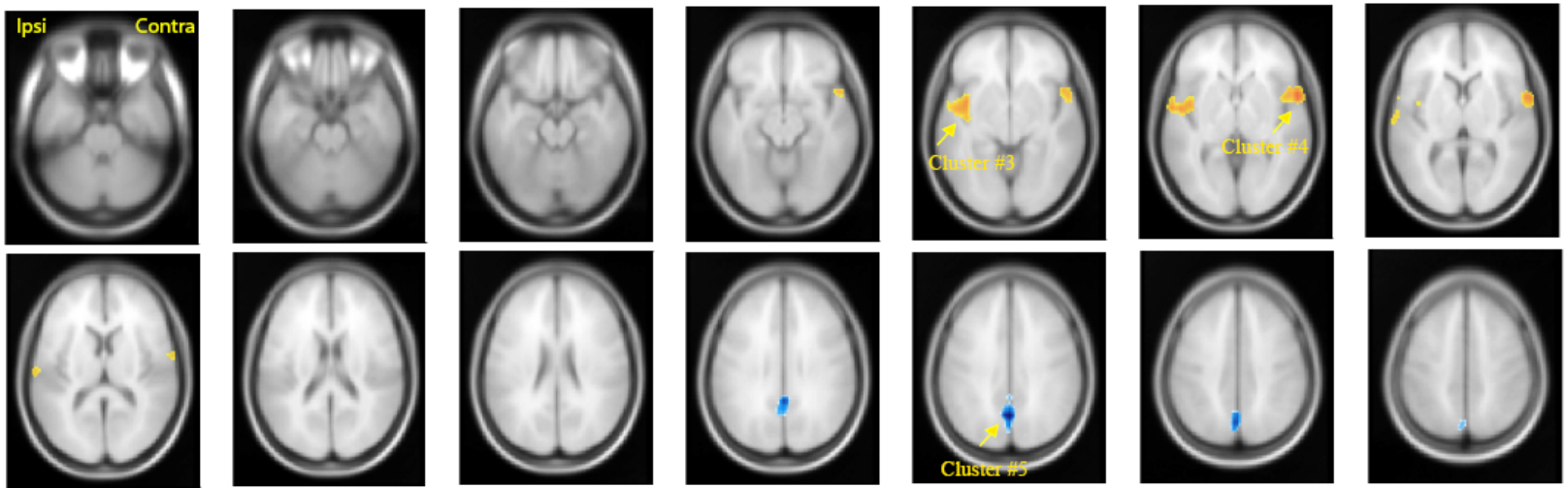
Kobayashi E., Grova C. et al. Epilepsia 2009

BOLD response to temporal spikes: Group analysis of 18 Temporal Lobe Epilepsy TLE patients

HRF: 3s after unilateral TLE spikes



HRF: 5s after unilateral TLE spikes



Discussion

- Multimodal concordance was found for spike generators localized in the focus as well as distant from the focus: **network?**
- fMRI results were more extended than EEG/MEG sources showing network involved even without neuronal synchronisation
- The fMRI clusters most concordant with EEG/MEG sources were the ones showing the most significant t-values
- Concordance with either BOLD activation or BOLD deactivation

What to do when no spontaneous epileptic discharges could be recorded during a 1hour session?

Can we learn something regarding the epileptogenic network from resting state functional connectivity ?

Outline

- Multimodal exploration of the epileptic network
- Group level analysis of functional connectivity in epilepsy
- Patient-specific functional connectivity patterns

Epilepsia, 53(6):1013–1023, 2012
doi: 10.1111/j.1528-1167.2012.03464.x

FULL-LENGTH ORIGINAL RESEARCH

Patterns of altered functional connectivity in mesial temporal lobe epilepsy

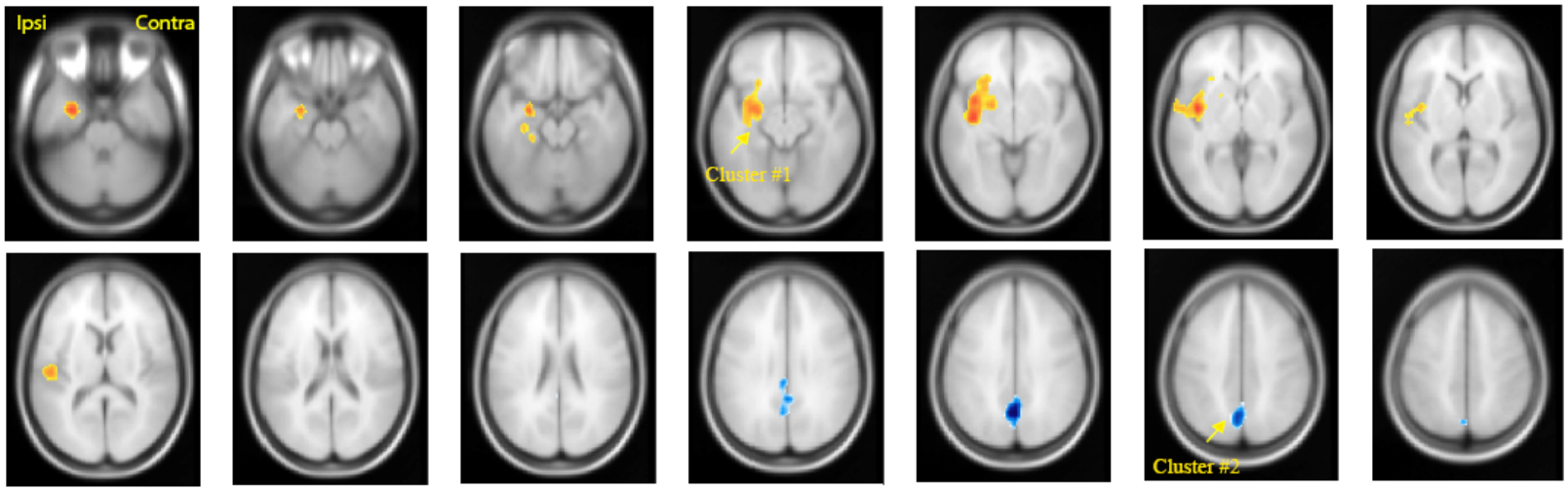
*Francesca Pittau, *†Christophe Grova, *Friederike Moeller, *François Dubeau and *Jean Gotman

- Mesial Temporal Lobe Epilepsy (MTLE)
  - epileptogenic area confined to the mesial temporal lobe
  - memory function is usually affected
  - but other cortical and subcortical areas are also affected and cognitive and psychiatric impairments are usually documented.

Kobayashi E., Grova C. et al. Epilepsia 2009

BOLD response to temporal spikes: Group analysis of 18 Temporal Lobe Epilepsy TLE patients

HRF: 3s after unilateral TLE spikes



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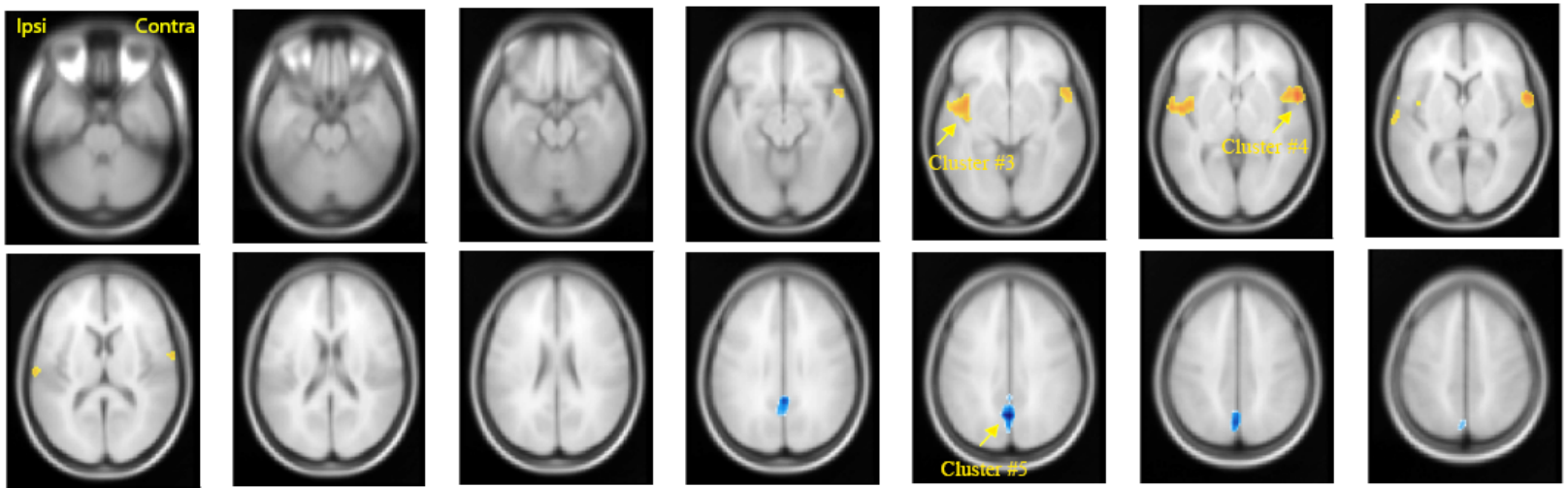


Objective of the study

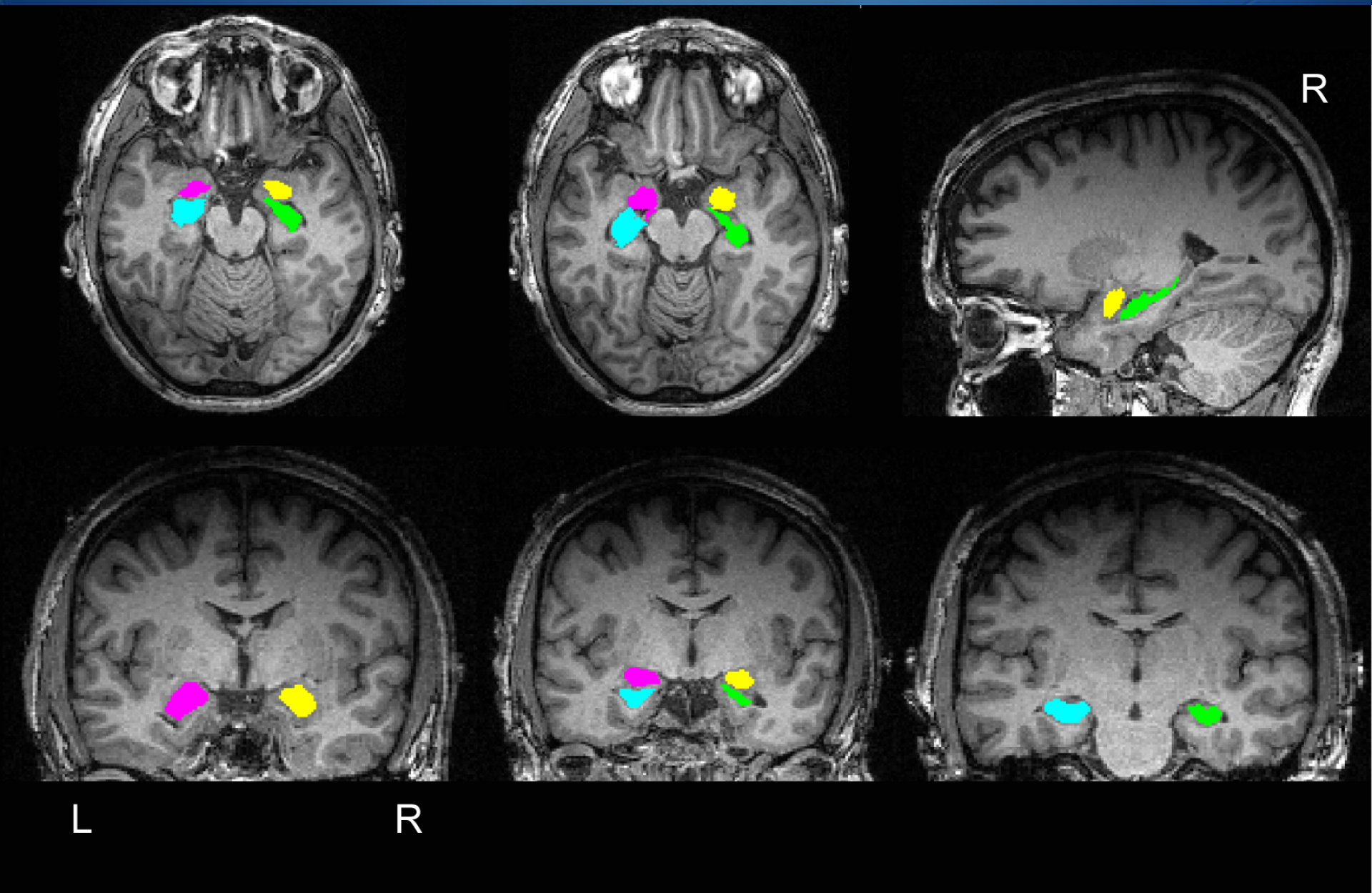
- To compare fMRI functional connectivity of MTLE patients during the interictal period with healthy subjects
- ***Hypothesis***: patients will show reduced functional connectivity compared to controls.

Methods

- Patients:
  - EEG-fMRI resting state data from 16 right and 7 left MTLE patients selected if
    - a) sections of fMRI recording free of EEG spikes
    - b) wakefulness
    - c) motion less than 1mm.
- Controls:
  - EEG-fMRI resting state data of 23 healthy subjects matched for age, sex and manual preference.

Methods

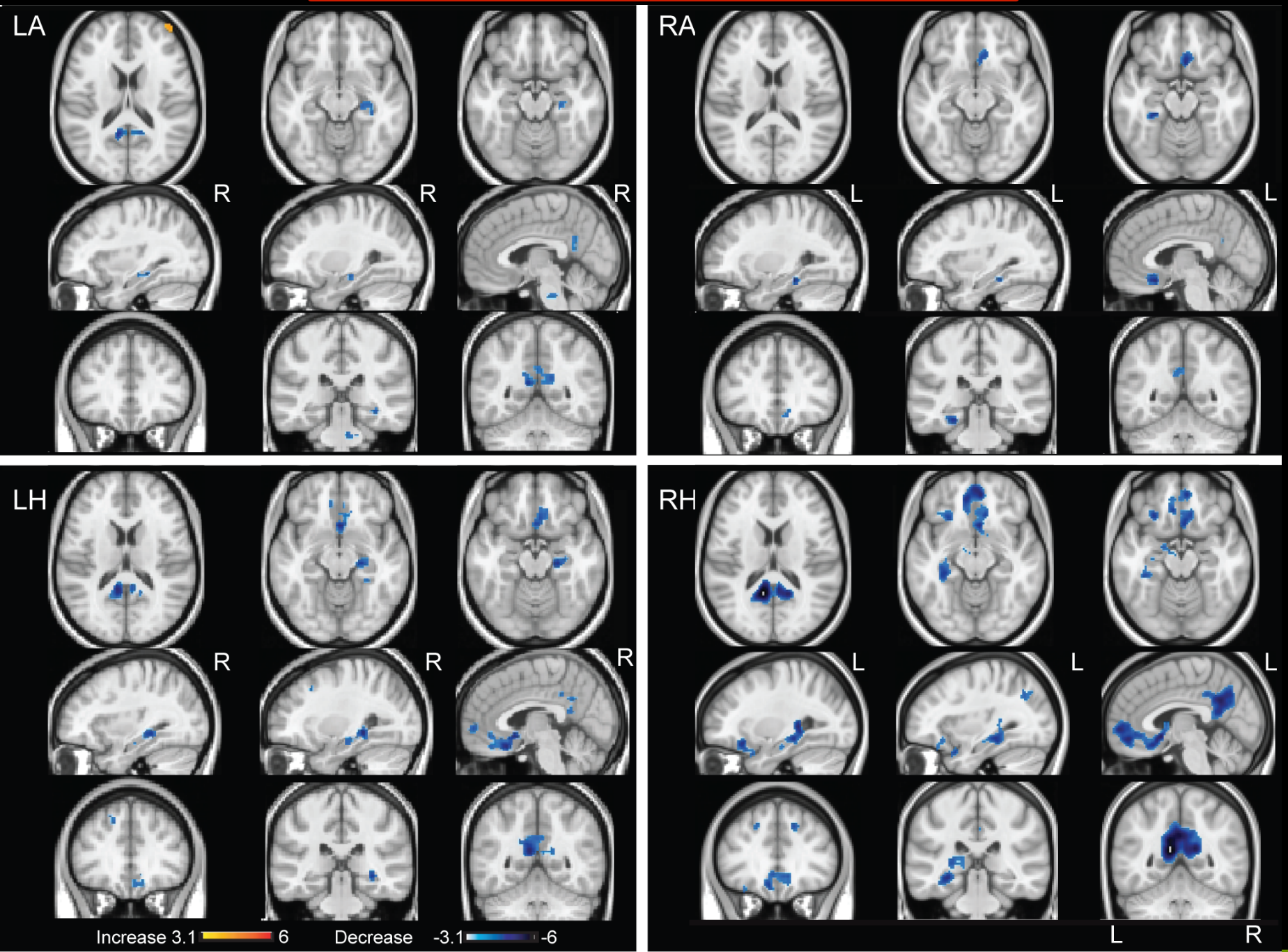
- Seed-based functional connectivity analysis
  - Four volumes of interest in the Left and Right Amygdalae and Hippocampi (LA, RA, LH and RH) were manually segmented in the anatomical MRI of each subject.


R
L
R

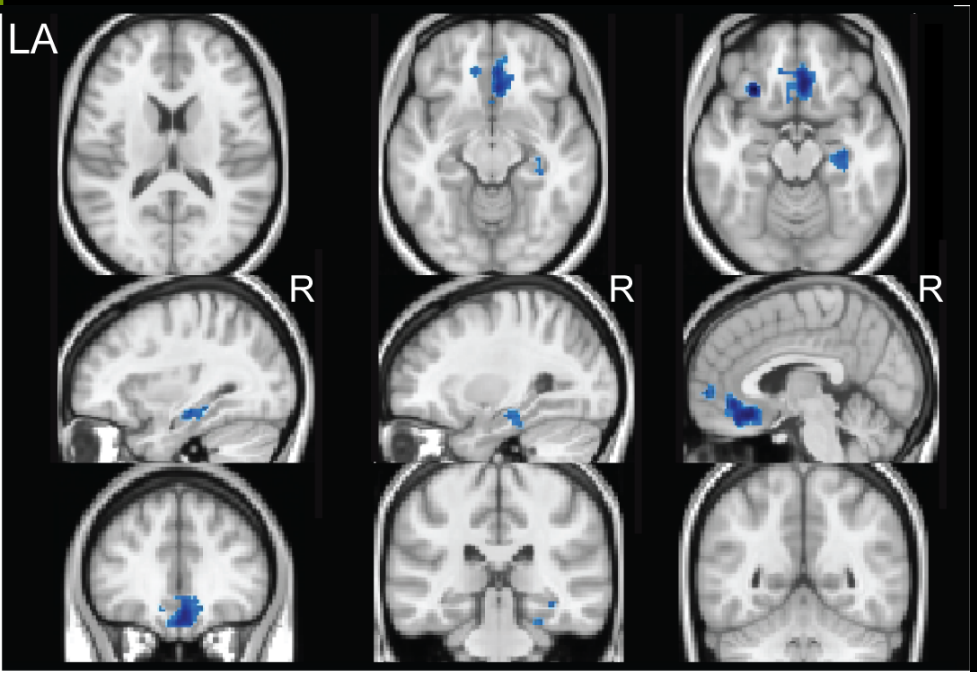
Methods

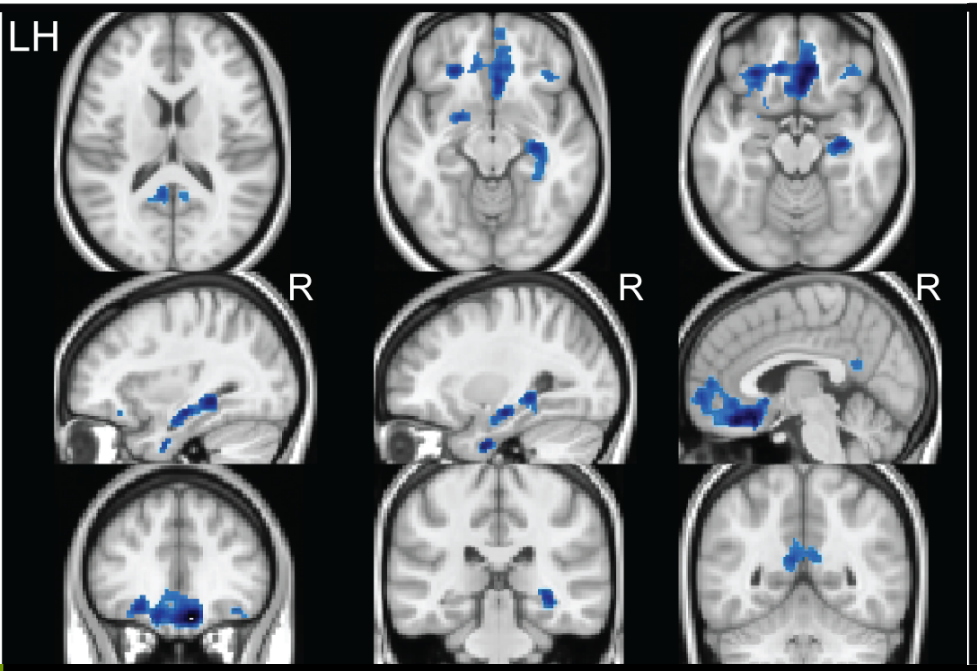
- fMRI data were corrected for physiological noise.
- The averaged BOLD time course within each volume of interest was used as a seed region to detect brain areas with BOLD signal correlated with it.
- Group differences between patients and controls were then estimated using a mixed effects model.

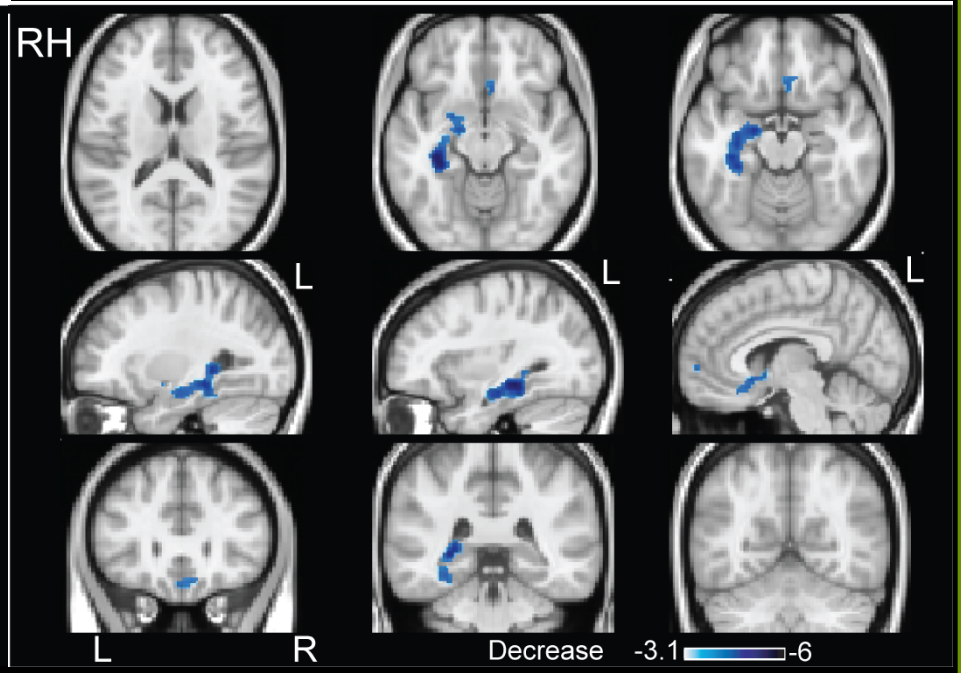
Right MTLE – controls group differences maps



Left MTLE – controls group differences maps







Discussion

- In unilateral MTLE, amygdala and hippocampus on the affected side, and to a lesser extent on the healthy side, are less connected:
  - between them
  - with the dopaminergic mesolimbic network
  - with the default mode network.
- Can these changes in functional connectivity explain cognitive and psychiatric impairments often found in patients with MTLE?

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Functional connectivity in patients with idiopathic generalized epilepsy

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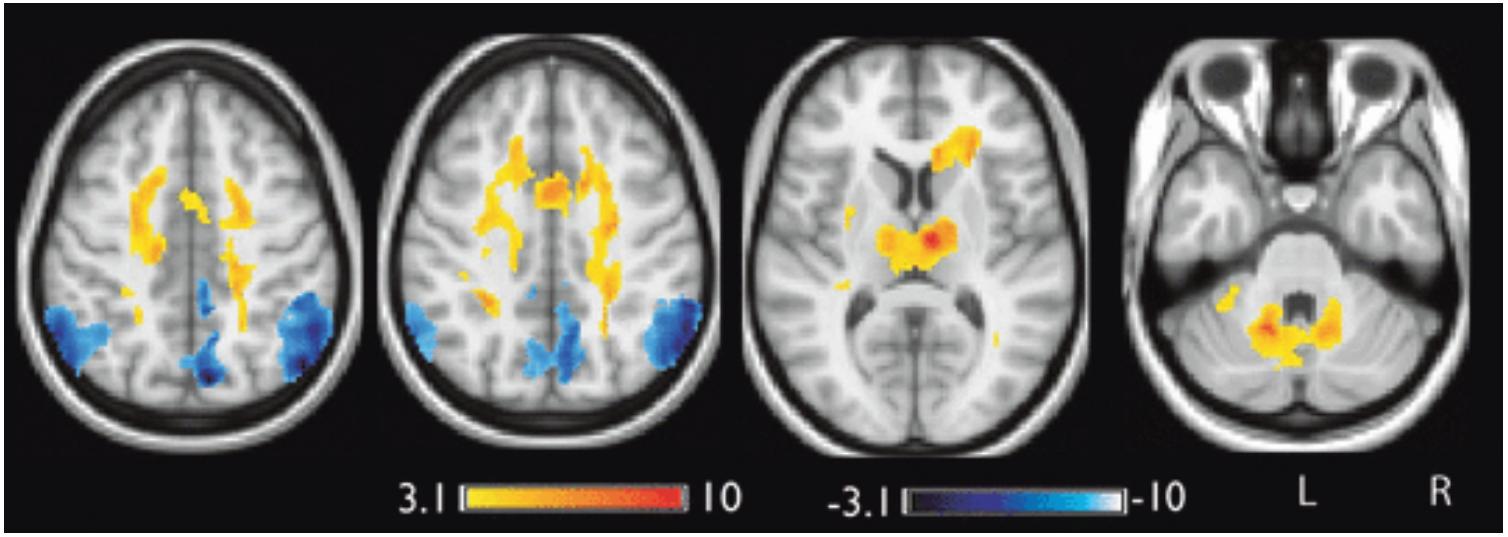
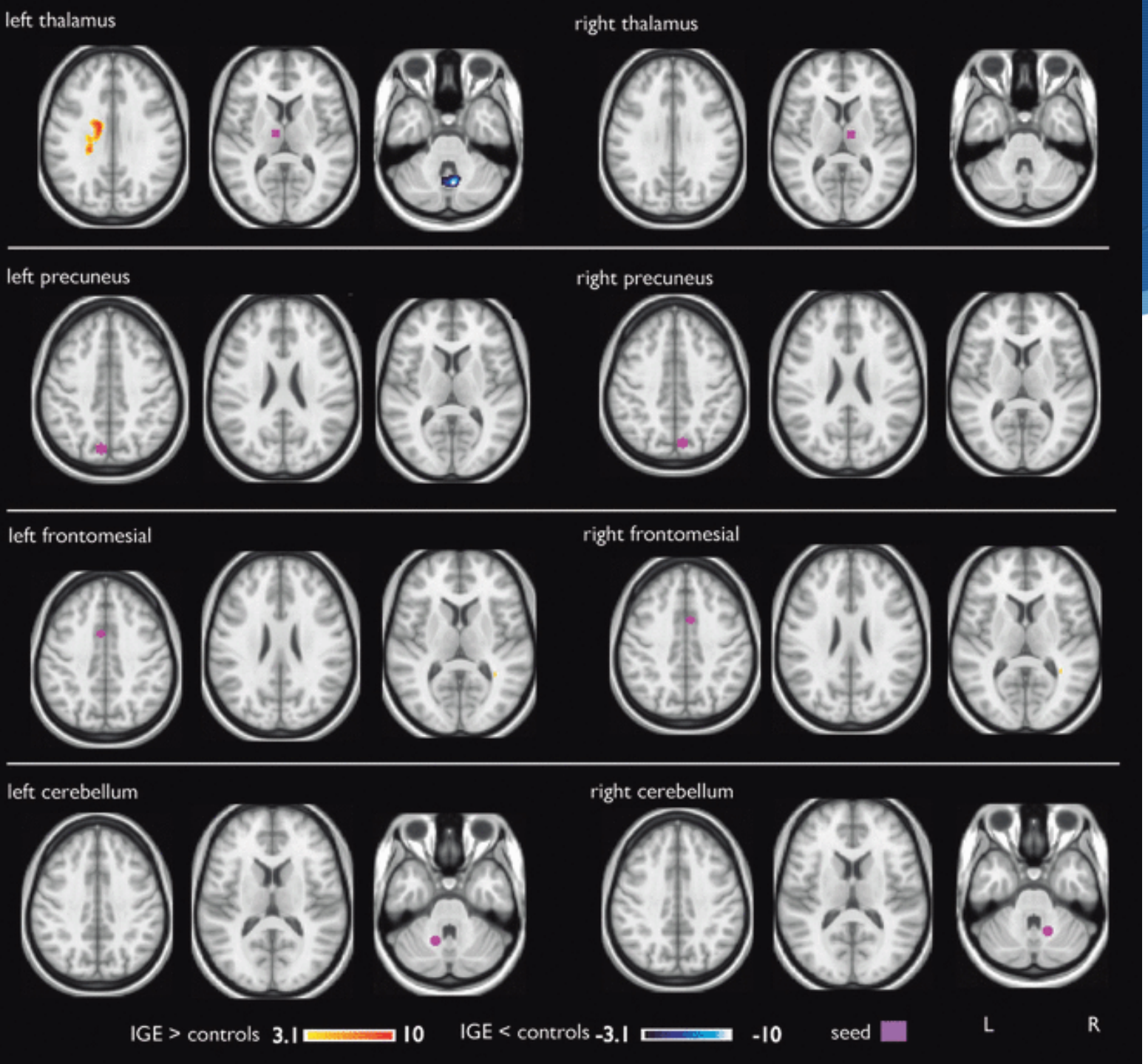


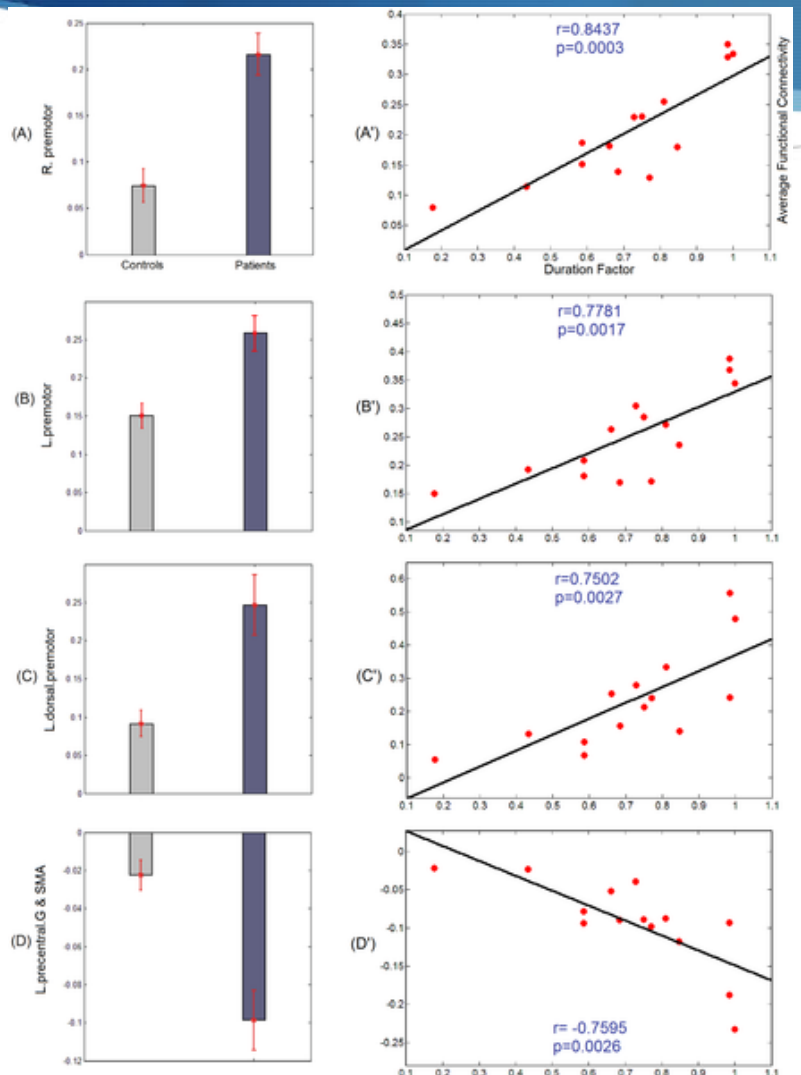
BOLD response to Generalized Spike and Wave discharges
Group analysis of 12 patients
Reproducibility of our main findings at 3T

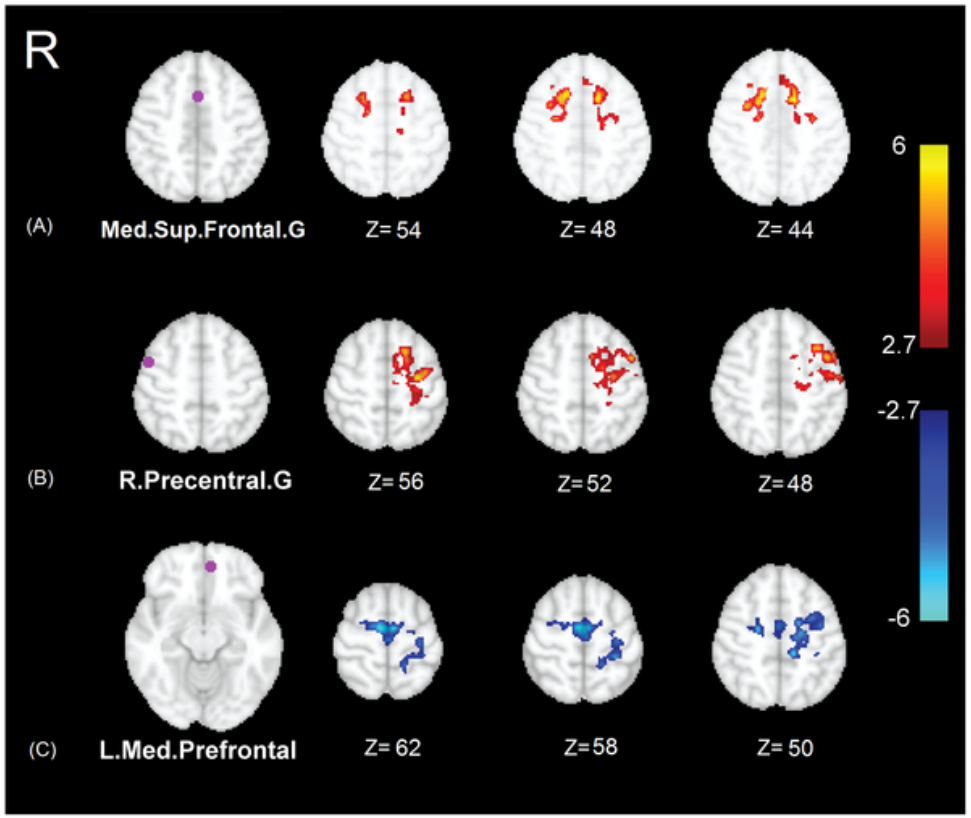


Seed-based Functional connectivity differences between 22 IGE patients and 30 controls

[Maneshi et al. PLoS ONE 2012]

Seed-based functional connectivity of the sustained attention network in Idiopathic Generalized Epilepsy (IGE)





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Shared and Specific Independent Components Analysis for Between-Group Comparison

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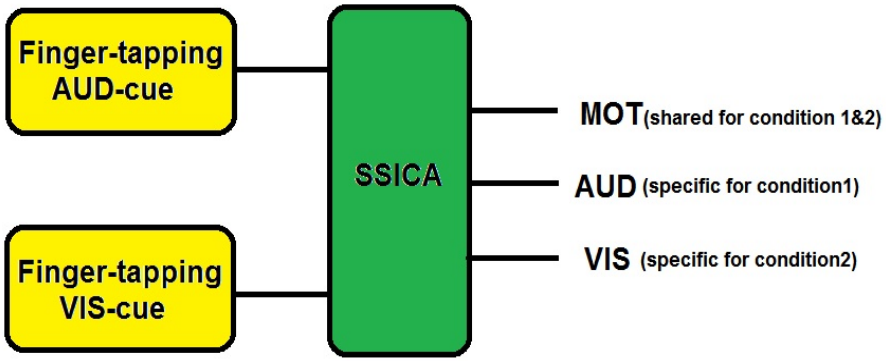
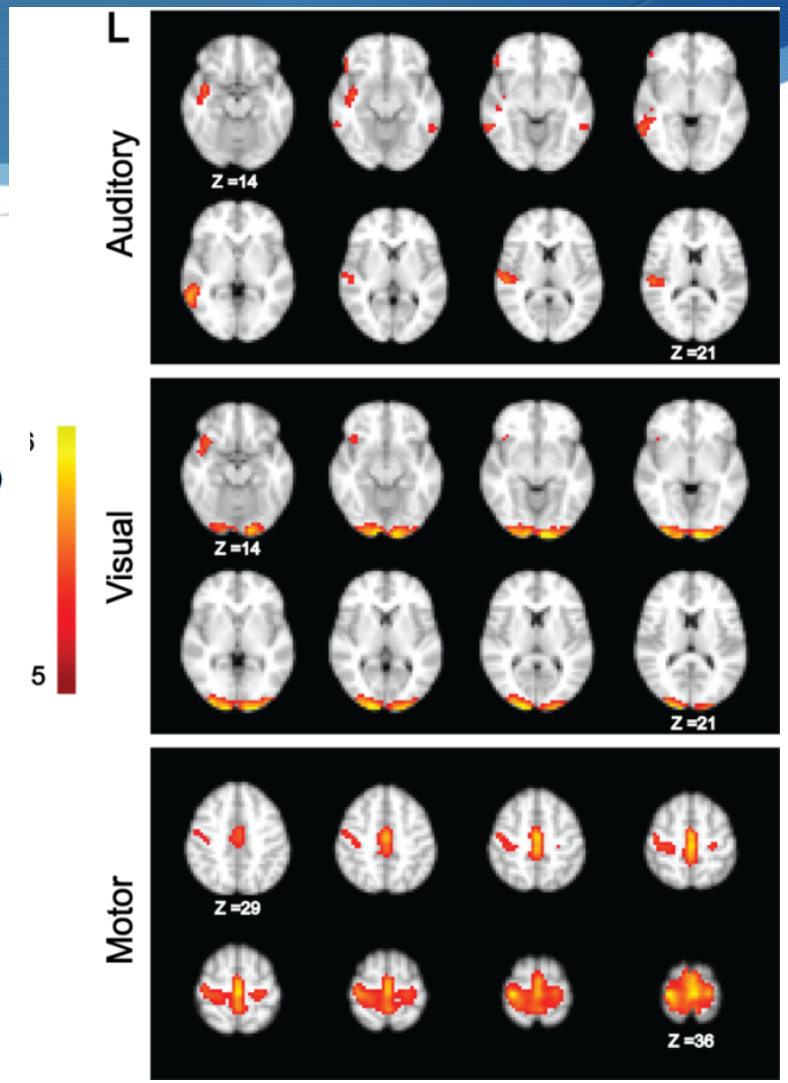
Shared (sh) and specific (sp) independent component analysis (SSICA) to extract and classify differences in brain networks between groups

$$\begin{bmatrix} X_1 \\ X_2 \end{bmatrix} = \begin{bmatrix} A_1^{sh} & A_1^{sp} & 0 \\ A_2^{sh} & 0 & A_2^{sp} \end{bmatrix} \begin{bmatrix} S^{sh} \\ S_1^{sp} \\ S_2^{sp} \end{bmatrix}.$$

[Maneshi et al, in preparation]

Shared and specific independent component analysis (SSICA) to extract and classify differences in brain networks between groups





Auditory specific cond #1

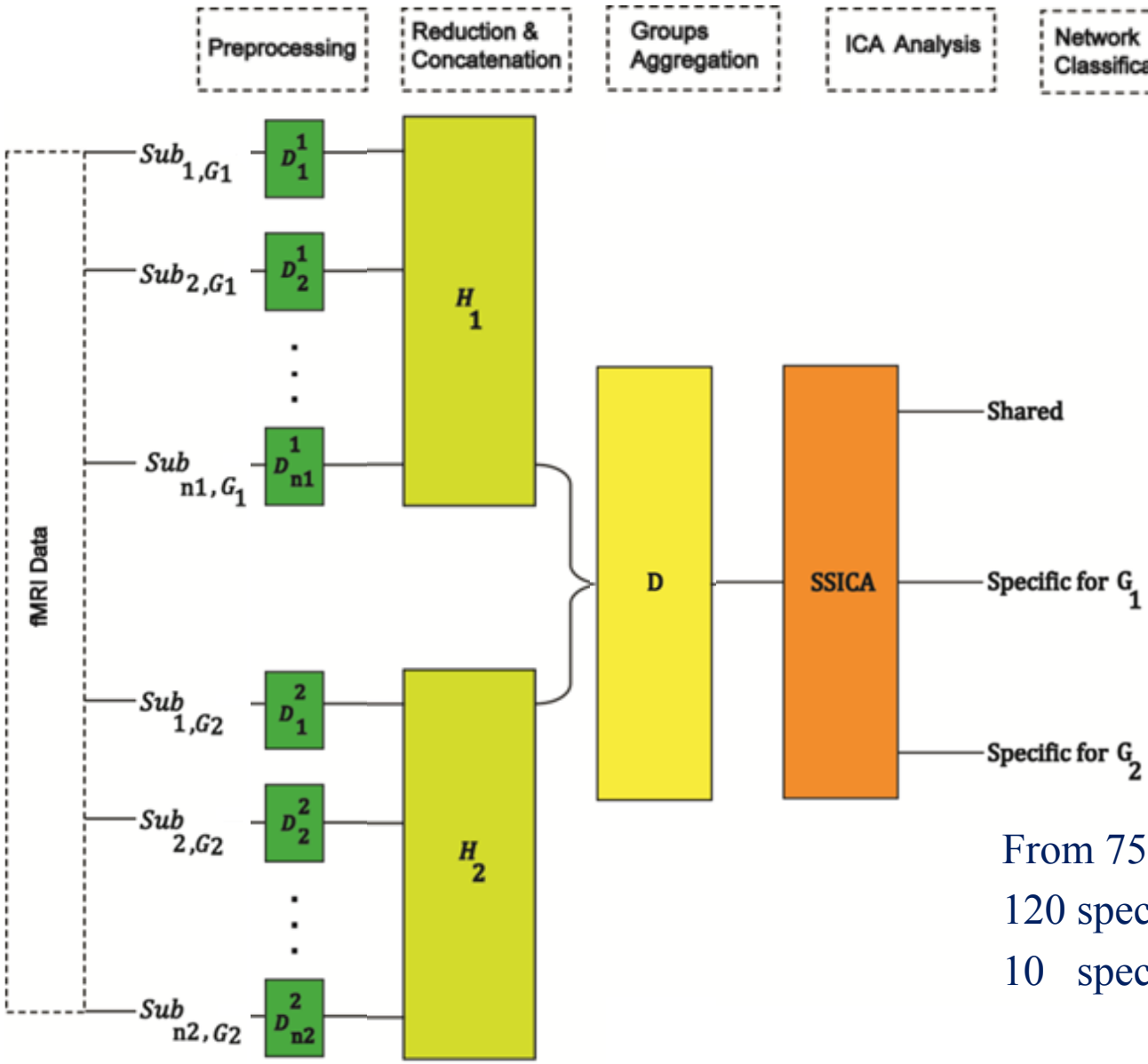
Visual specific cond #2

Motor shared

Method

- 14 controls and 14 IGE patients
- 3T scanner, 24 min of resting-state functional MRI
- In patients, only data from wakefulness without epileptic discharges
- Regular preprocessing (cardiac and respiratory artefacts removed) as described in [Maneshi et al. PLoS ONE 2012]
- SSICA to extract shared and specific networks for both groups

SSICA Method



Main parameters of SSICA

# of specific networks for G1

# of specific networks for G2

Consistency analysis

several runs of SSICA by varying these parameters + clustering

From 75 SSICA runs:

120 specific networks for patients

10 specific networks for controls

[Vahdat et al, Neural Comp 2012]

[Maneshi et al. in preparation]

Discussion

- FC analysis based on the seeds in areas involved during GSW discharges [Moeller et al. Epilepsia, 2011] did not show clearly altered FC for patients versus controls.
- FC analysis based on the seeds in areas involved in visual sustained attention [Maneshi et al. PLoS ONE , 2012] demonstrated that alterations of FC in IGE patients are not limited to the frontal areas. However, patients with long history of disease show changes in FC mainly within the frontal areas.
- Using SSICA, IGE patients were found to have 2 specific networks, none for to healthy controls.
- Network A includes premotor, primary motor, and somatosensory cortices, medial prefrontal cortex, and bilateral caudate and thalamus.
  - ***Network A seems to be related to the generation/propagation of GSWs in IGE***
- Network B includes parts of the posterior and anterior cingulate gyri, premotor and supplementary motor cortex and precuneus.
  - ***Network B seems to be related to the attention problem in this population.***

Discussion

- In MTLE and IGE, detection of decreases or increases in functional connectivity patterns even in absence of epileptic discharges
- Suggesting regions exhibiting impaired metabolism, especially but not only, within the epileptogenic network and even when no epileptic discharges could be detected: in agreement with PET hypometabolism.
- Resting state functional connectivity as a biomarker in epilepsy ? Detection methods at the ***individual level*** should be developed and validated.

Outline

- Multimodal exploration of the epileptic network
- Group level analysis of functional connectivity in epilepsy
- **Patient-specific functional connectivity patterns**

[Dansereau et al. in revision]

Proposed methodology: DANI
Detection of Abnormal Networks in Individuals

- **Statistical framework**: identification of stable consistent resting-state networks (CRSNs)
  - Consensus clustering in order to identify stable networks:
    BASC: Bootstrap Analysis of Stable Clusters, Bellec et al. Neuroimage 2010
  - Statistical stability and reproducibility both at the group and at the individual level

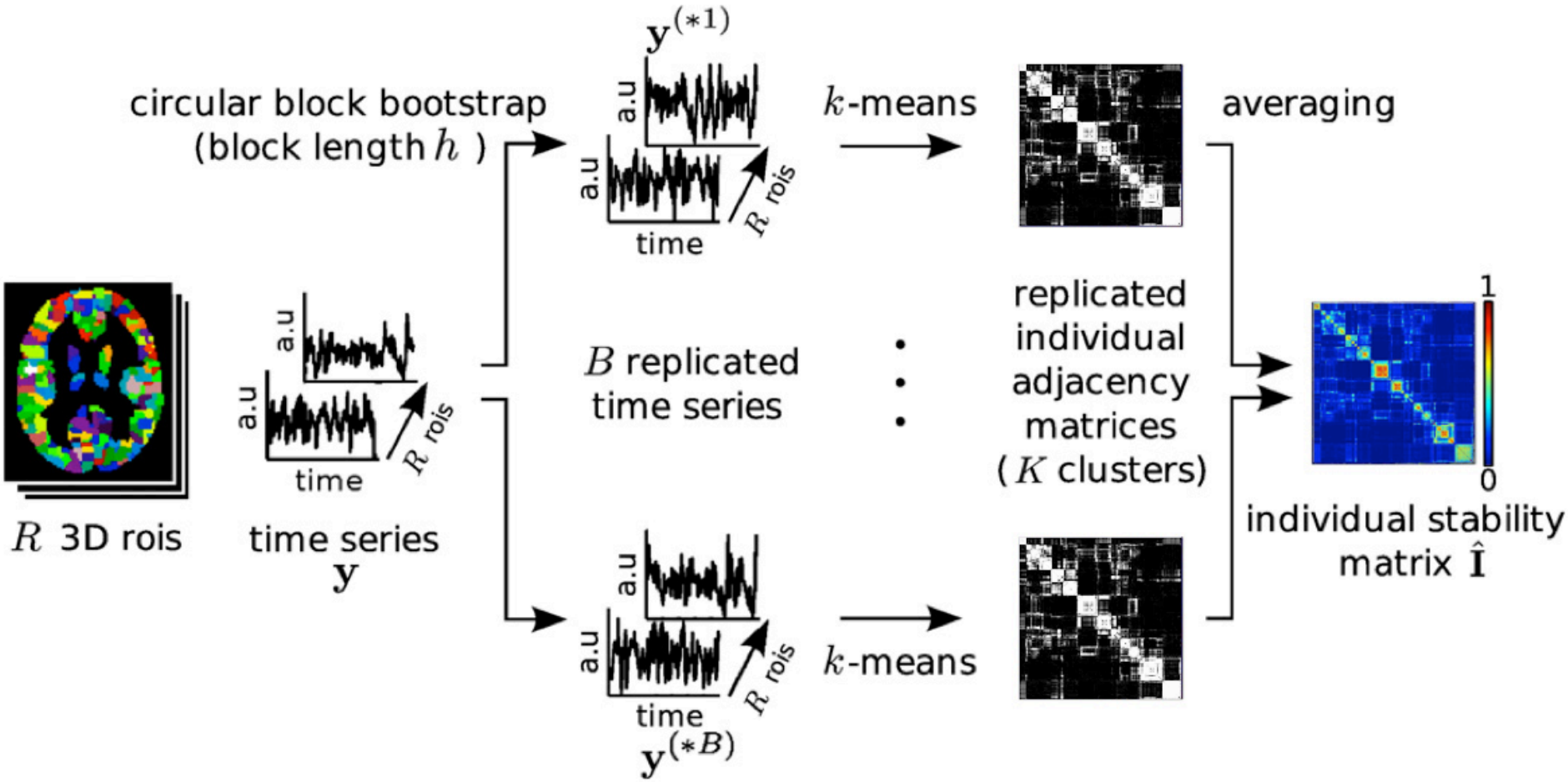
- **Detection of abnormal networks in individuals**
  - ***Hyp: We will consider as "abnormal" networks, the stable resting state networks identified at the individual level considered as outliers when compared to a population of healthy controls***
  - DANI aims at detecting modularity changes at the individual level by focusing on the changes in connectivity within the cores of each networks

Method

BASC
(Bootstrap Analysis of Stable Clusters)
Pierre Bellec
(Multi-level bootstrap analysis of stable clusters in resting-state fMRI, NeuroImage 2010)

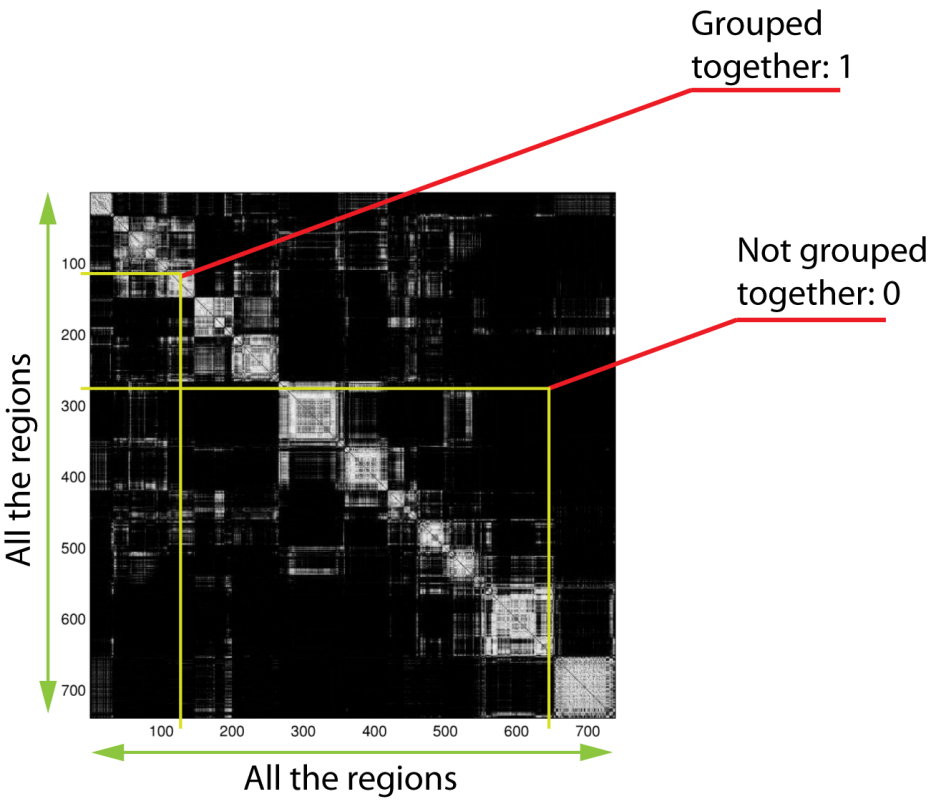
BASC individual-level

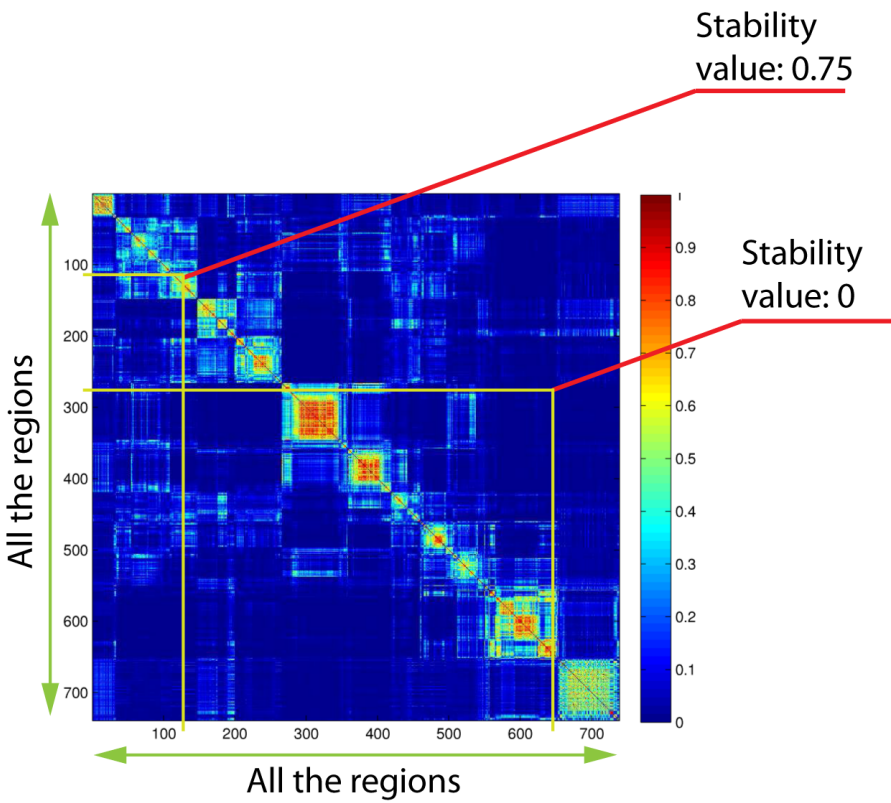
P. Bellec et al. / NeuroImage 51 (2010) 1126–1139



BASC individual-level

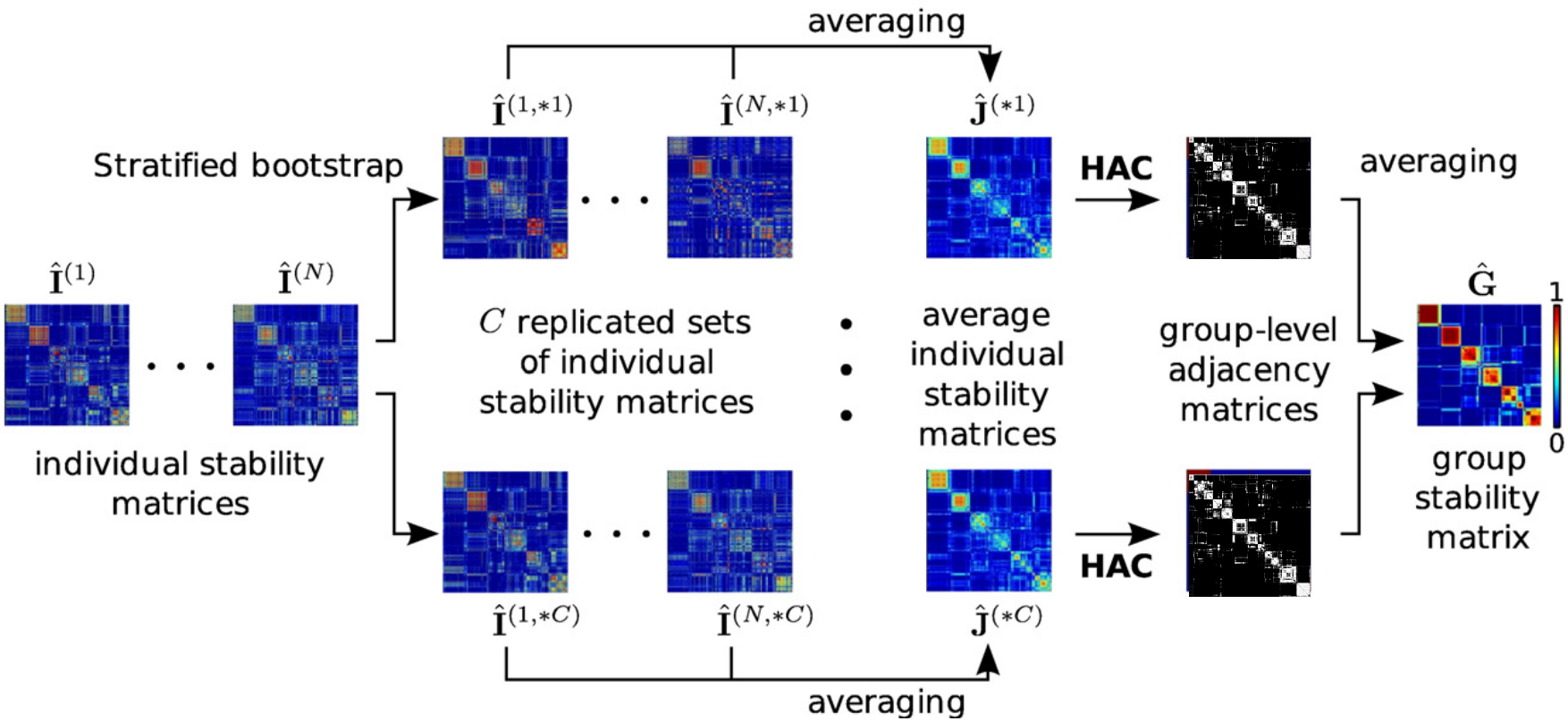
The resulting stability matrix is a statistical measure indicating how often two regions hav been classified within the same cluster





BASC group-level

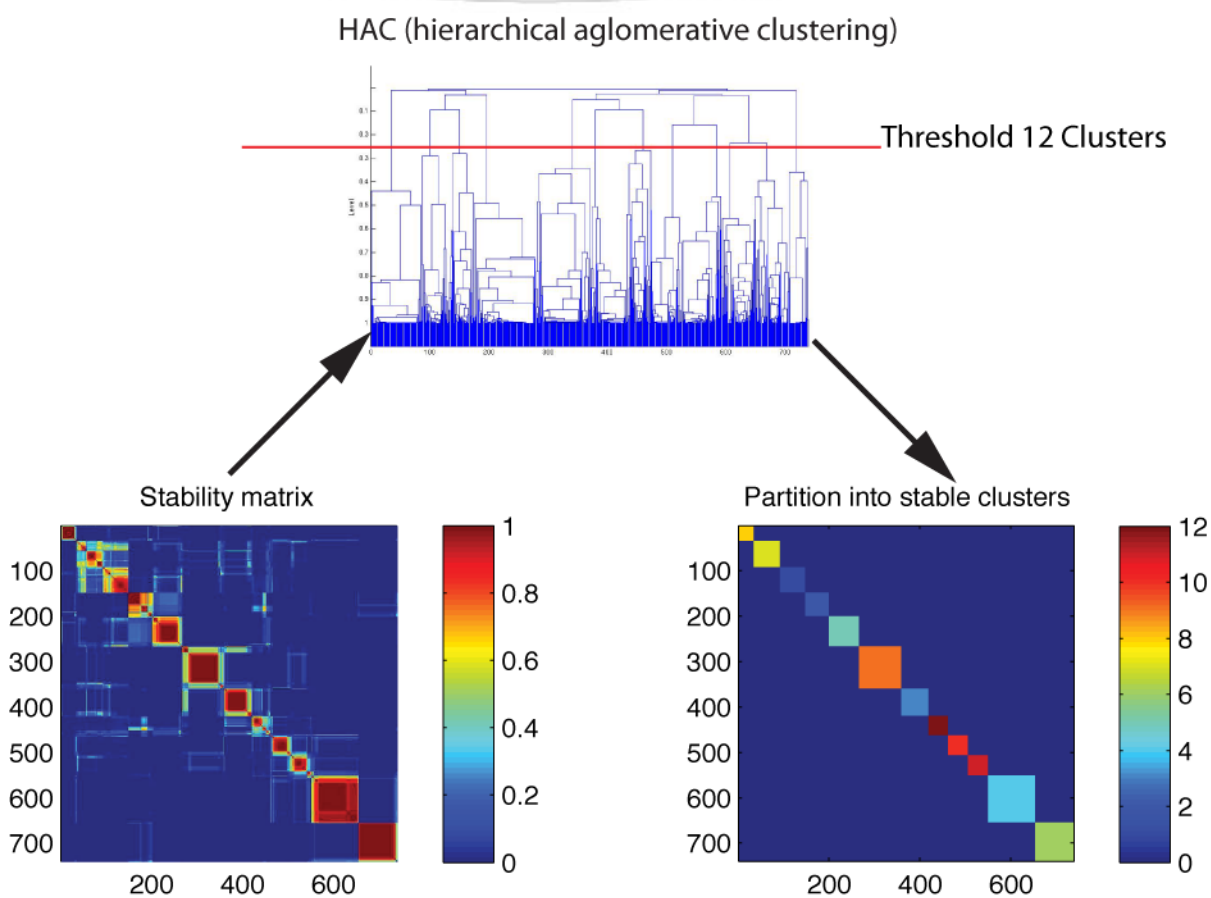
P. Bellec et al. / NeuroImage 51 (2010) 1126–1139



Method: subject versus group analysis

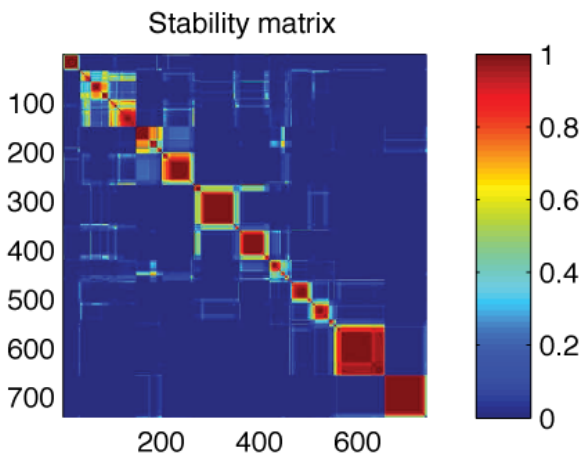
- We now have stability matrices at the individual and group level
  - We need to partition the matrix into networks.
  - We need to convert stability matrices into 3D maps.
  - Find a metric to identify the significant changes in the stability map.

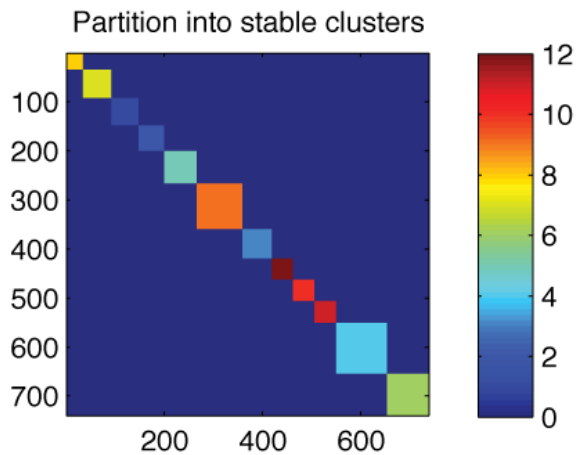
Partition: consensus clustering at the group level



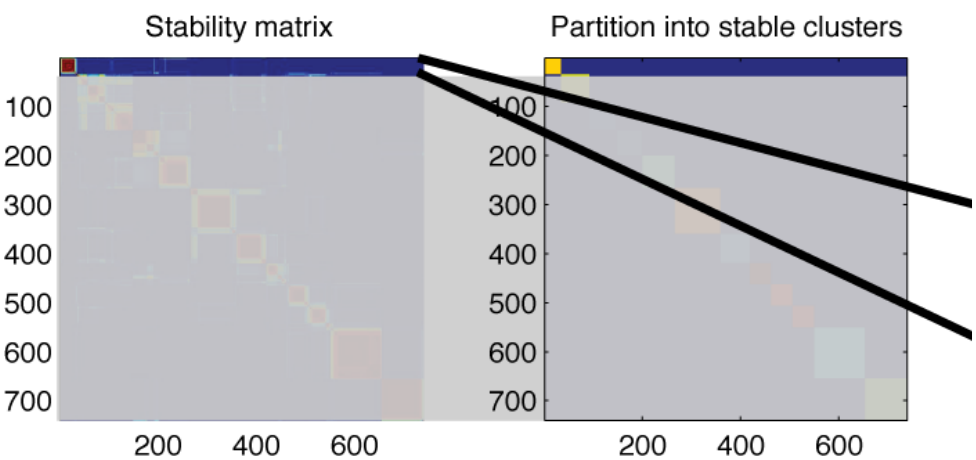
- The literature is referring to around 7 – 10 consistent RS networks.
- We decide to threshold at 12 to be sure that we do not miss any important cluster.

Stability maps





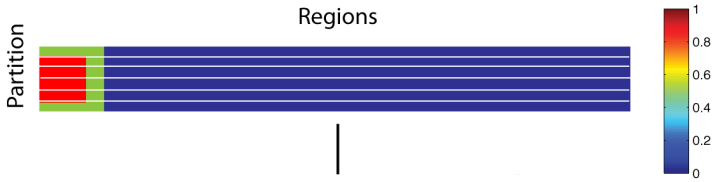
- We need to convert the matrix into a 3D map of the brain.



Extension of BASC to extract abnormal networks in individuals

Stability maps

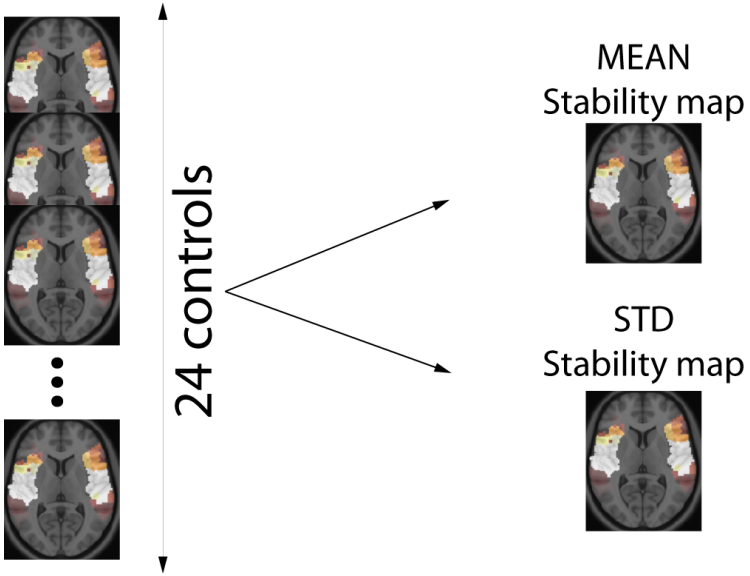
Average stability
of the entire partition



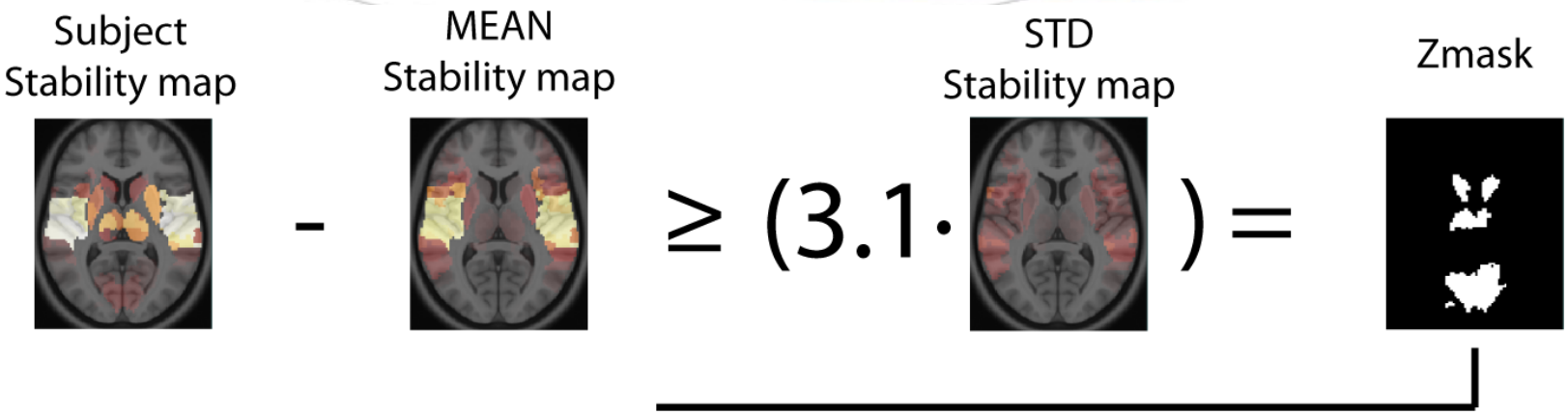
- To be flexible at the individual level, while being informed by the group level partition
- Focus on the regions constituting the core of the networks to improve the contrast.

Detection of significant changes in individual matrices

- To detect significant changes at the individual level.
  - **We first need to apply the partition from the group analysis on the individual stability matrices.**
  - It will result in the individual stability networks.
- **Detection problem:** 1 subject vs. group (24 controls)
- Keep in mind that the **measure of stability is a statistical measurement**.

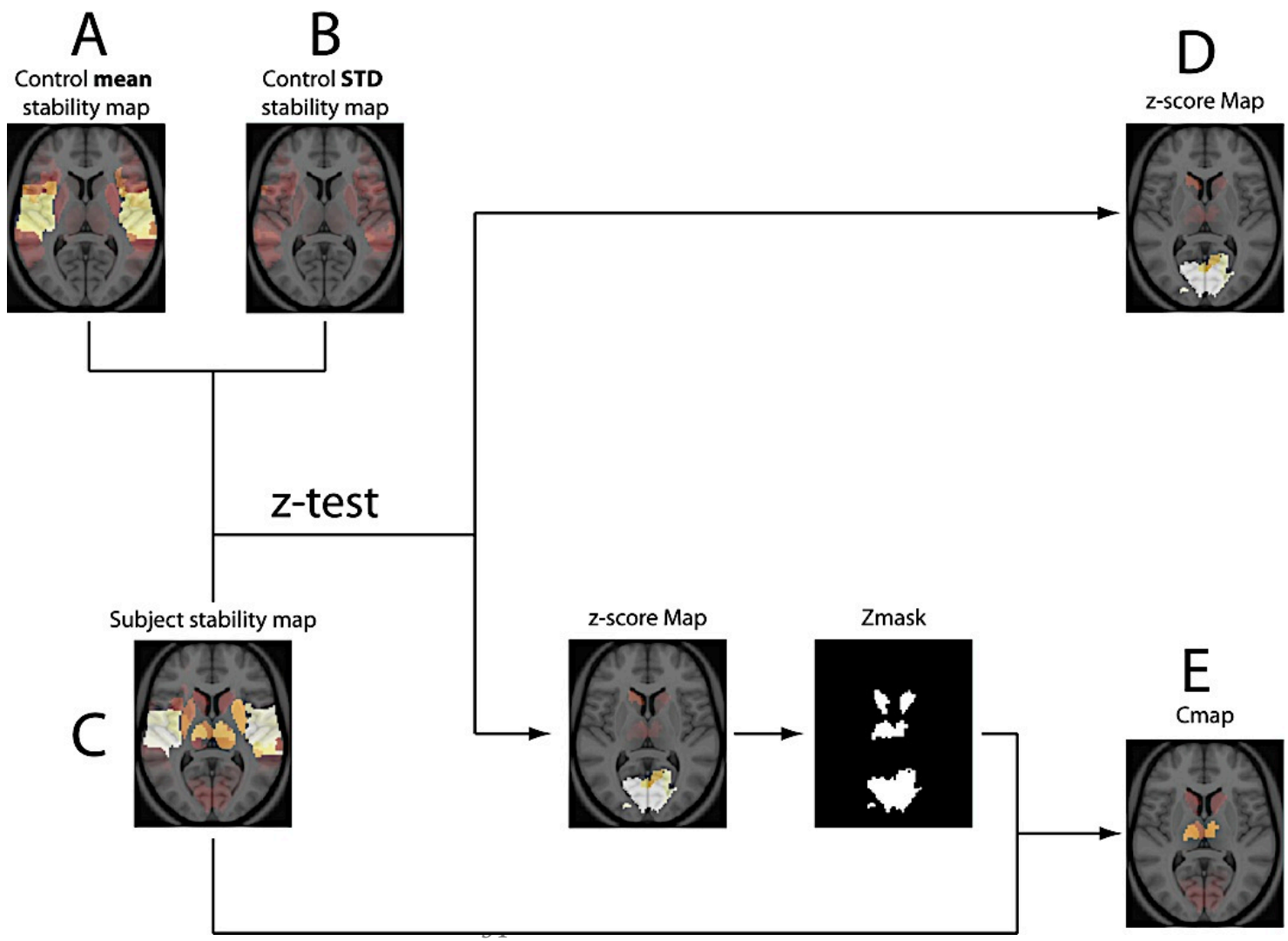


Combined map of stability changes



- Solution
  - Isolate the area of major changes with a Z-score mask.
  - Combine the Zmask and the stability map.
  - Resulting in a map of the major changes in stability: modularity changes within the cores of each network

Combined stability map versus Z-score map



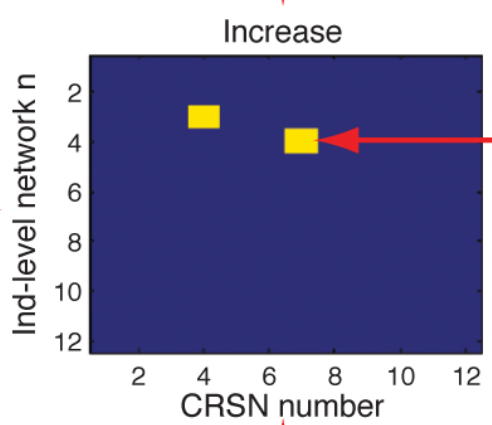
Comparison metrics

- **Metric 1: network volume changes:** % of volume belonging to each group level CRSN within the individual level network (spatial extent)
- **Metric 2: stability strength:** average stability within the overlap area associated with Metric 1
- Metric 1 and Metric 2 were estimated:
    - For each individual level network (12 networks)
    - For increases in stability when compared to controls
    - For decreases in stability when compared to controls

Abnormal network detection

Increase or decrease in stability

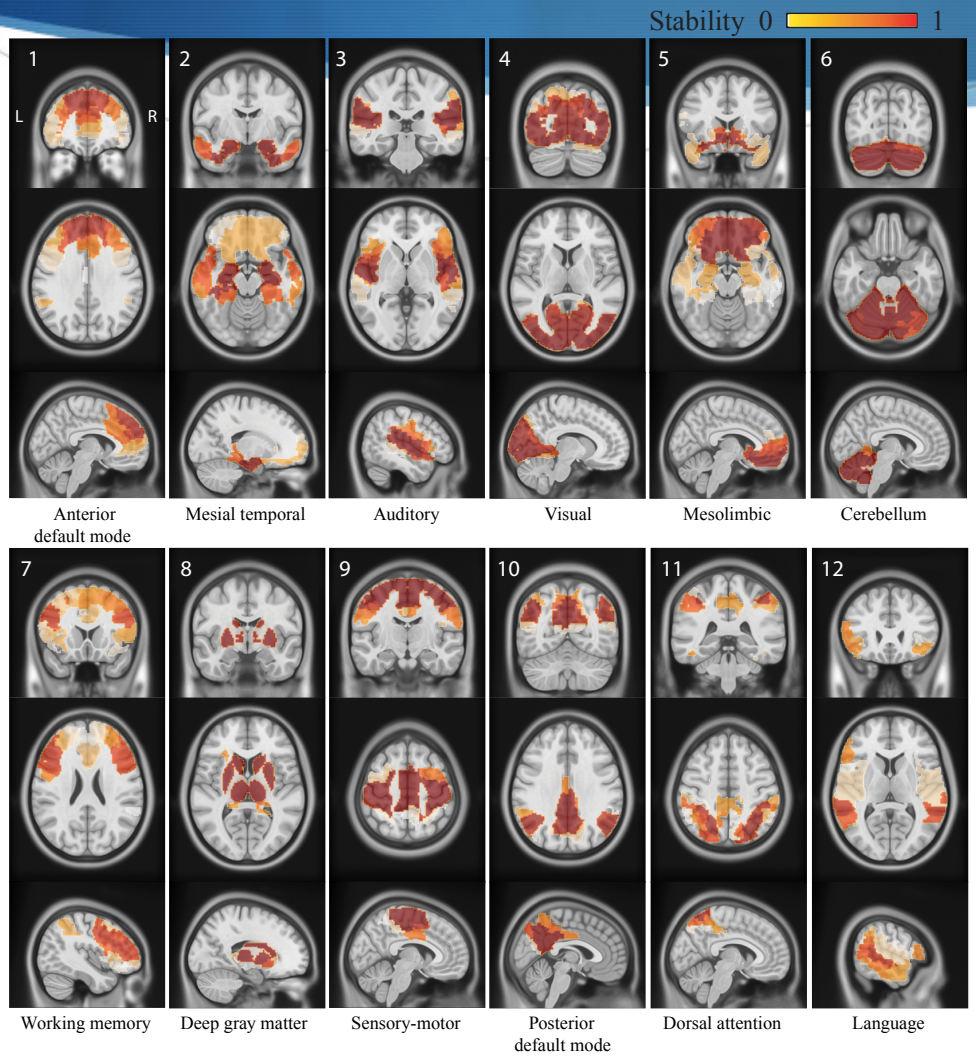
Individual analysis



Significant values
(non parametric p<0.001)
compared to the Null distribution
The Null distribution is obtained
by pooling all 12x12 values for
all the 24 controls.

CRSN interaction

Bootstrap Analysis of Stable Clusters (BASC, Bellec et al Neuroimage 2010)

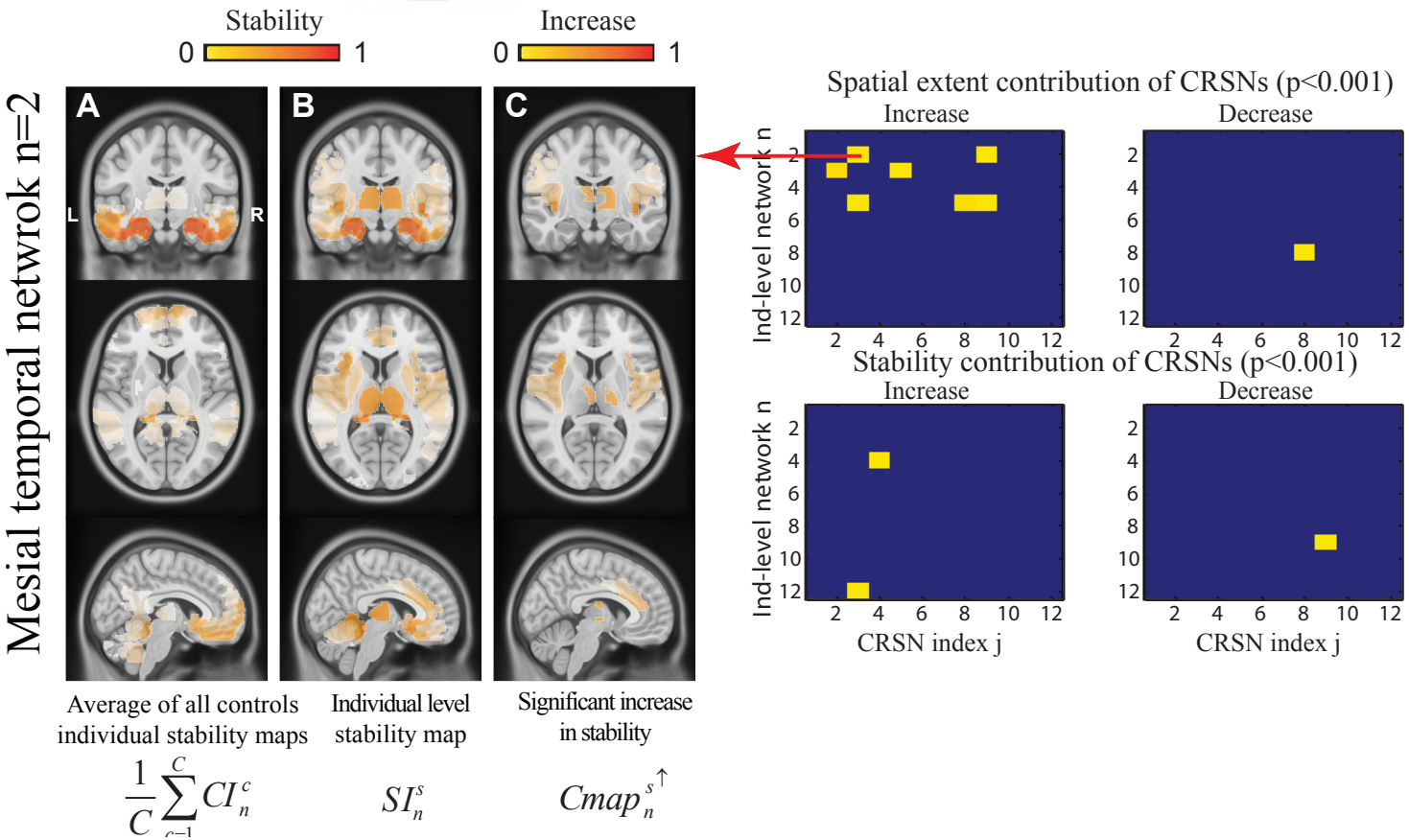


BASC measures a statistical stability of the clustering for each Resting State network at both **Group** or **Individual** levels

Reproducing BASC results into 12 CRSNs from a data base of 24 controls

[Dansereau et al. in revision]

DANI result on 1 patient with temporal lobe epilepsy: Detecting "abnormal" networks at the individual level = "outliers" networks when compared to a population of controls



Discussion

- DANI is robust to random and structured noise interference
- Preliminary results on clinical data:
  - Some patients may exhibit "normal" RSNs
  - Some patients exhibit some "abnormal" networks, suggesting reorganization in "agreement" with the underlying epilptogenic network
- Clinical validation is required
- Impact of the spatial scale of the CRNs, should we use a patient-specific scale?
- Non-stationnary aspects: EEG during EEG/fMRI acquisitions

Discussion and perspectives

- **Functional connectivity using fMRI:** importance of group-level versus individual analysis
- Functional connectivity provides insights from **ongoing normal and pathological brain activity** even when no epileptic discharges could be recorded (**biomarkers?**)
- Looking for electrophysiological signatures: **wavelet-based Max Entropy on the Mean** (Lina et al IEEE TBME 2012) seems particularly adapted to study **sources localized from resting state EEG/MEG data in different frequency bands**
- Applying the proposed methodology to EEG/MEG data to detect normal and « abnormal » resting state networks, taking into account the 1/f structure
- **Key issues:** spatial scale, non stationnarity
- ***Multimodal characterization the link between ongoing bioelectrical activity and hemodynamic fluctuations in resting state networks***

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