Michele Allegra [#], Chiara Favaretto, Maurizio Corbetta, Andrea Brovelli

Stroke-related alterations in inter-areal communication revealed via Granger causality analysis

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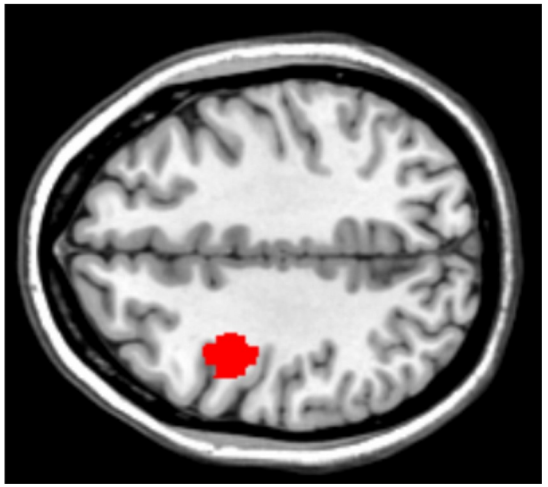
Overview

- Motivation
    - What we can learn on stroke from neuroimaging
- Methods
    - Covariance-based Granger Causality
- Results
    - Intra- and inter-hemispheric GC anomalies

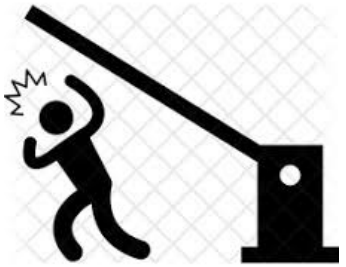
Basic phenomenology

focal lesions



widespread behavioral deficit

motion



attention

speech

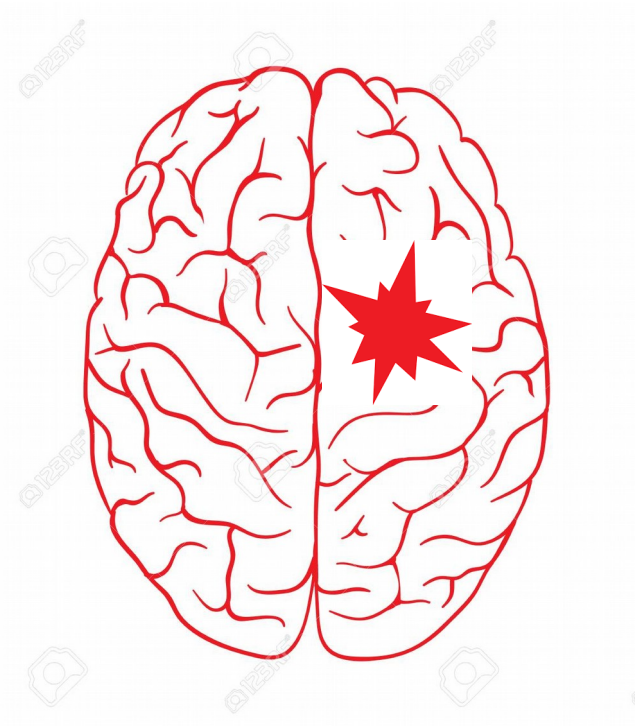
memory

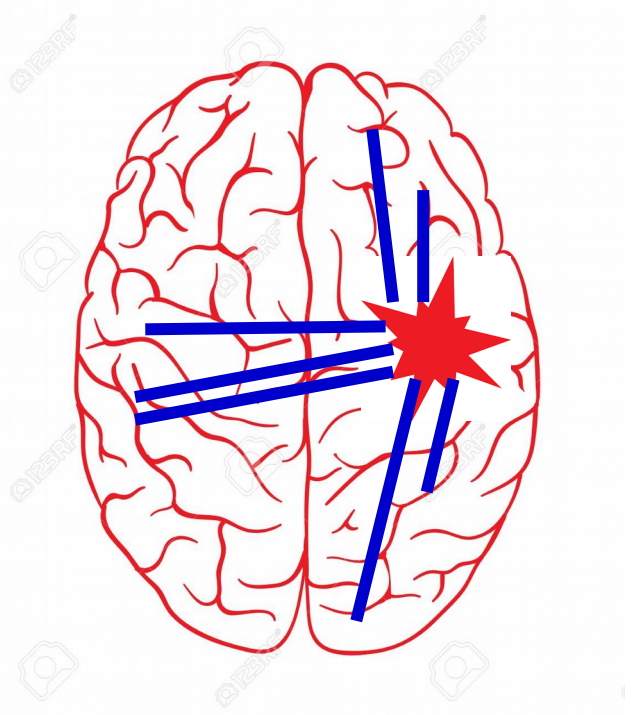
Stroke

structural **damage at site of injury**

widespread **network dysfunction**

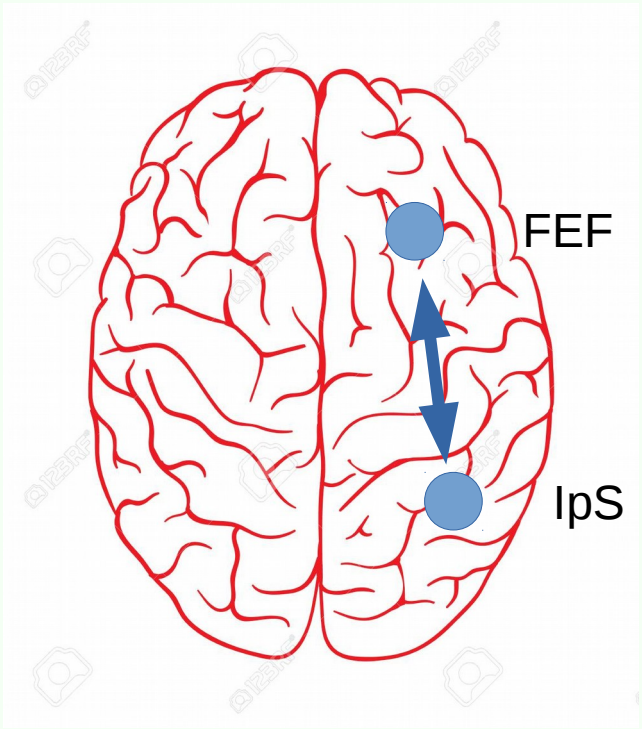
deficit





Stroke

structural **damage at site of injury** → deficit ← widespread **network dysfunction**



Spatial attention

Exploration/orienting — Frontal eye field

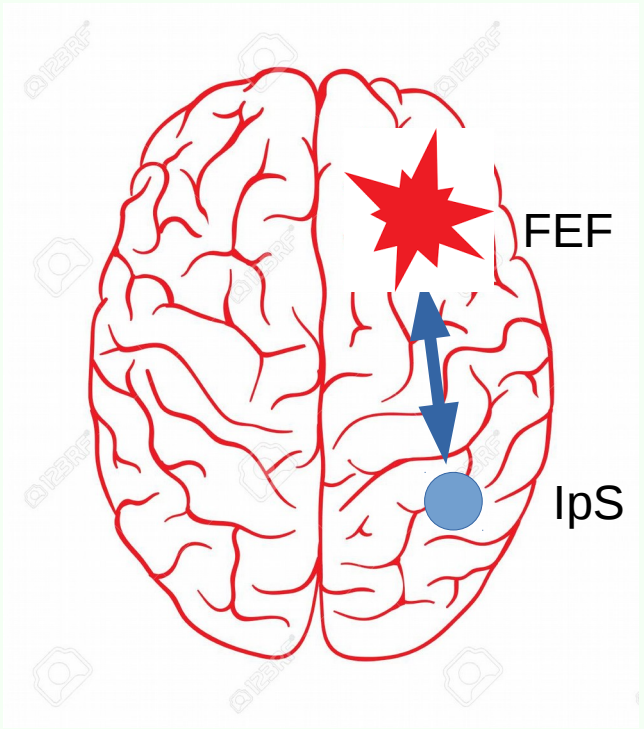
Space representation — Intraparietal sulcus

Stroke

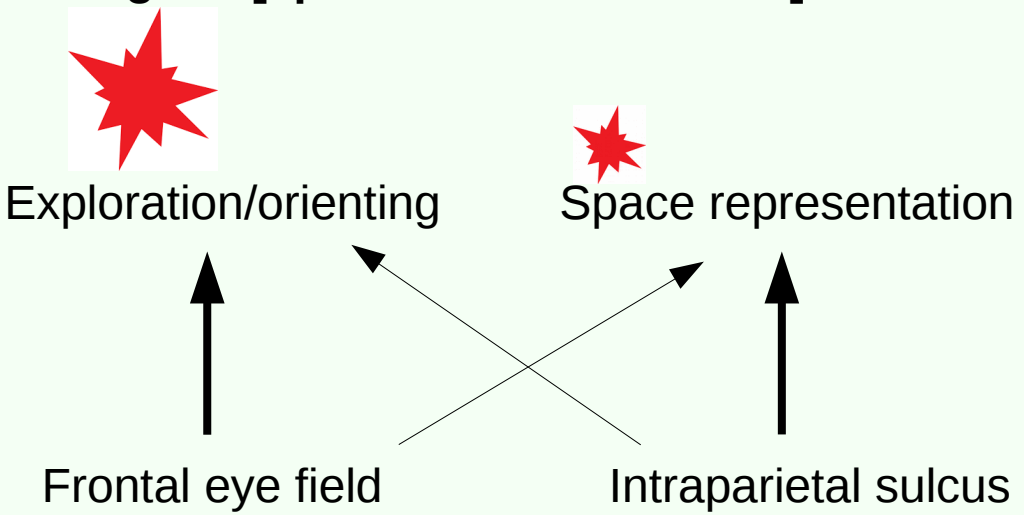
structural damage at site of injury

widespread network dysfunction

deficit



Neglect [spatial attention deficit]

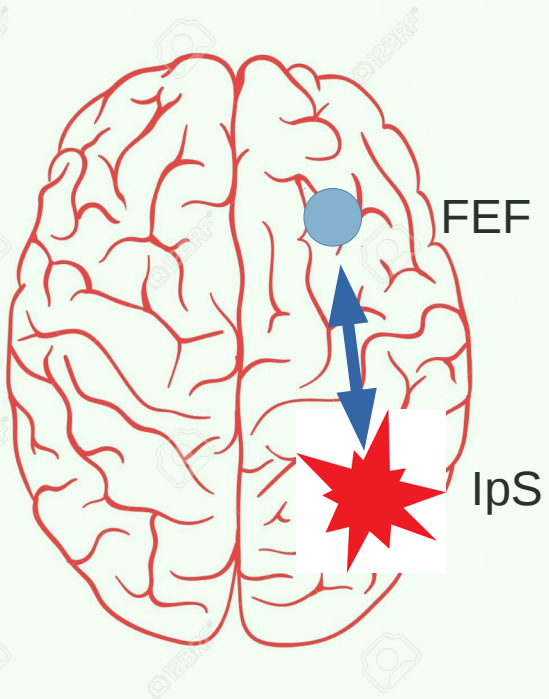


Stroke

structural damage at site of injury

widespread network dysfunction

deficit



e.g. neglect [spatial attention deficit]

Exploration/orienting

Space representation

Frontal eye field

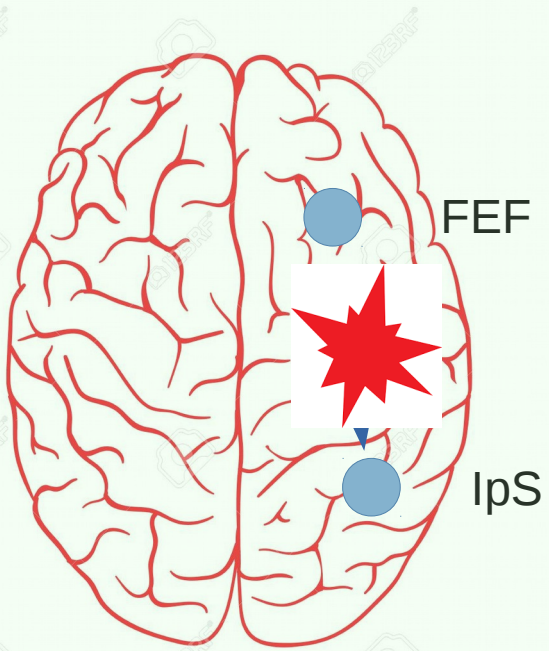
Intraparietal sulcus

Stroke

structural damage at site of injury

widespread network dysfunction

deficit



e.g. neglect [spatial attention deficit]

Exploration/orienting

Space representation

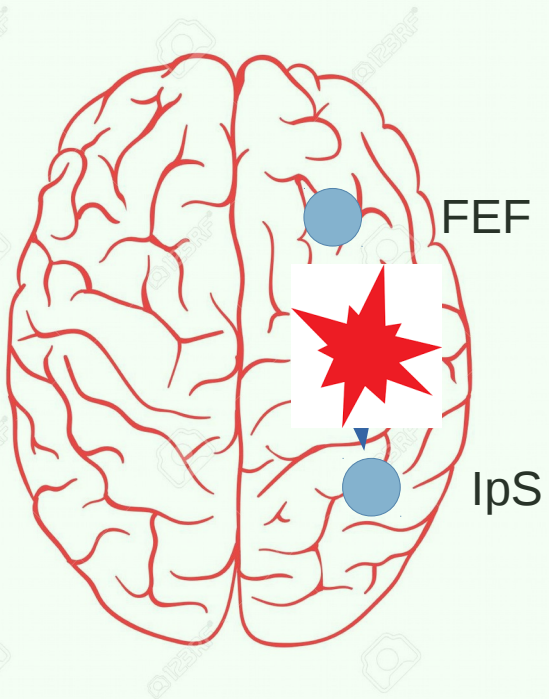
Frontal eye field

Intraparietal sulcus

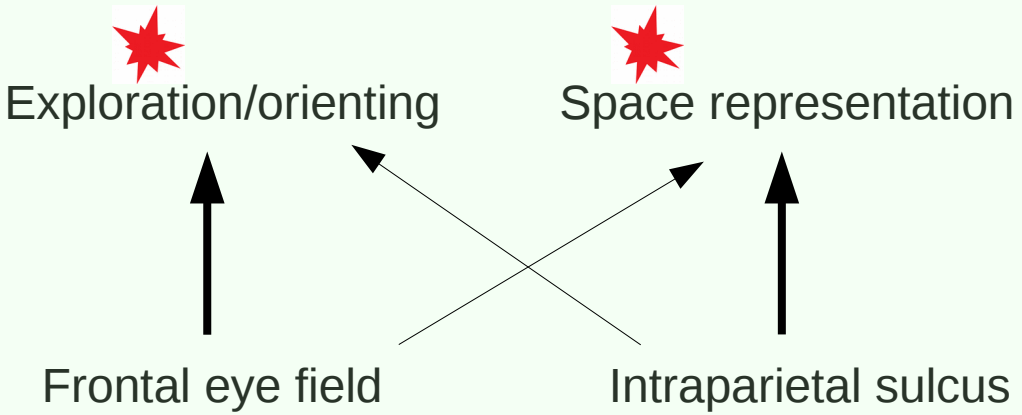
Stroke

Focal lesions impair on large-scale distributed brain networks, impacting on both local processing and inter-areal communication

… neuroimaging strengthens this network perspective and the relevance on inter-areal communication...



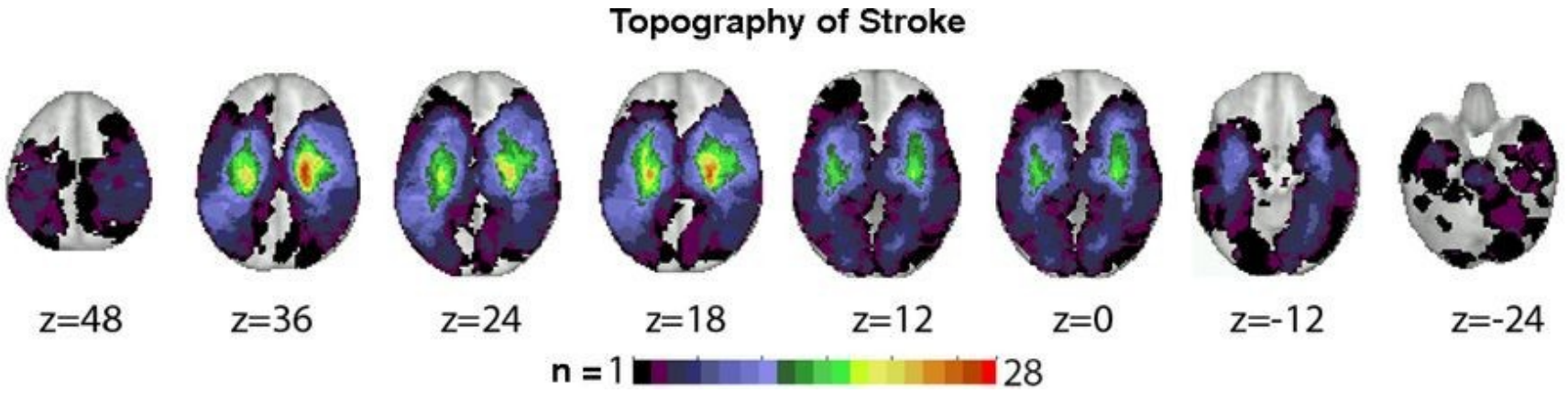
e.g. neglect [spatial attention deficit]



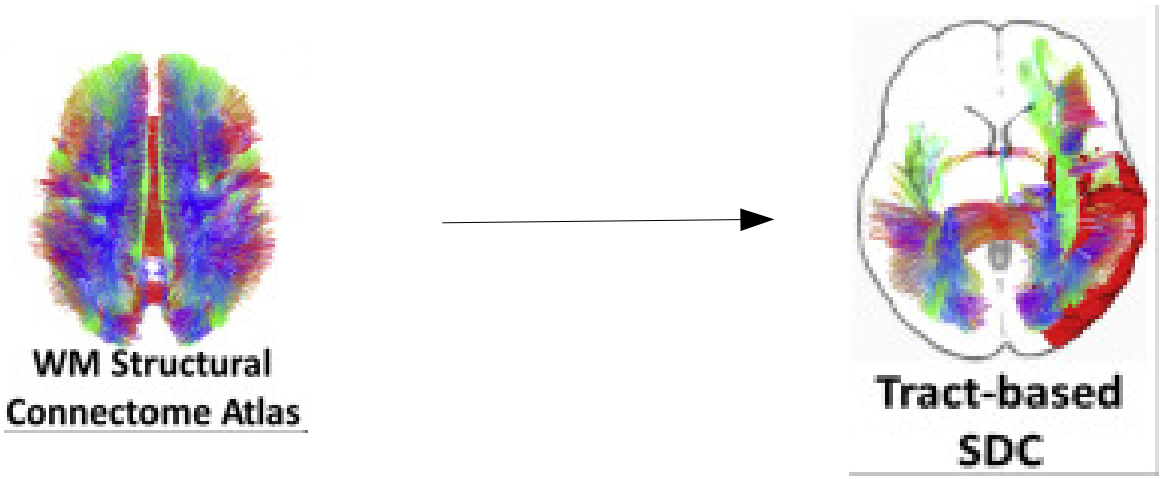
What can we learn by neuroimaging?

1) Structural topography of lesions

Stroke affects subcortical white matter and nuclei



Structural connections between brain areas are severly affected

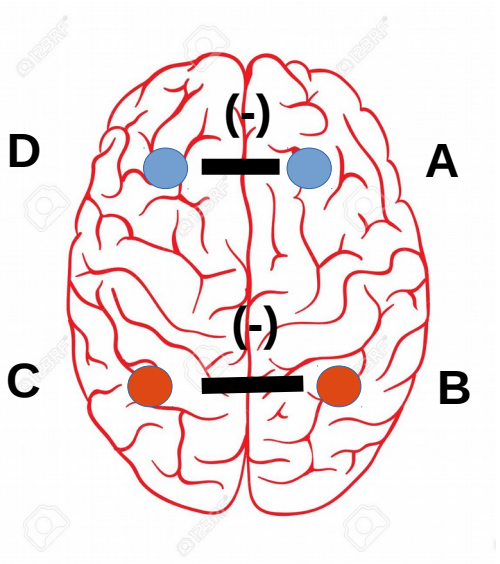


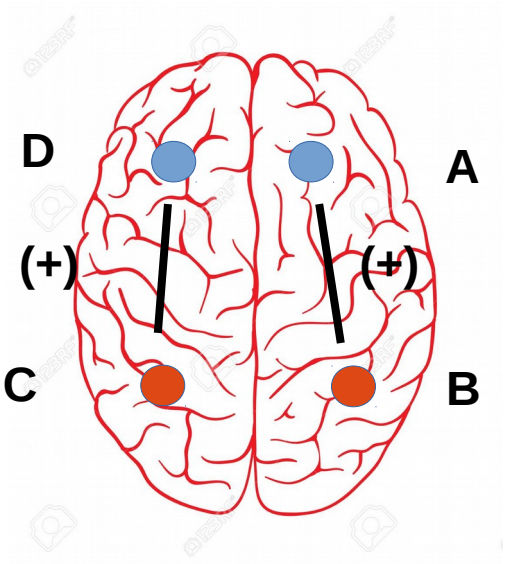
J Griffis et al. Cell reports 28.10 (2019): 2527-2540.

What can we learn by neuroimaging?

2) functional disconnection effects

analyses via resting-state functional connectivity [Siegel, …., Corbetta., PNAS 113.30 (2016)]





motor network

dorsal attention network

decrease of FC between homologous areas [same network]

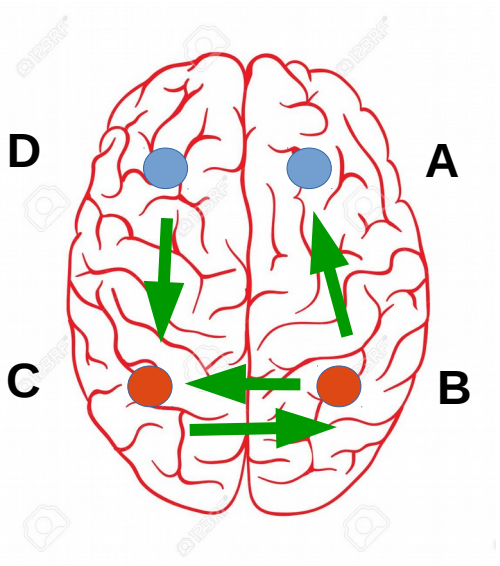
increase of FC between homologous areas [different networks]

FC disruptions predict behavioral deficit better than lesion location

What (else) could we learn by neuroimaging?

3) effects on inter-areal communication

analyses via resting-state ***directed connectivity***



?

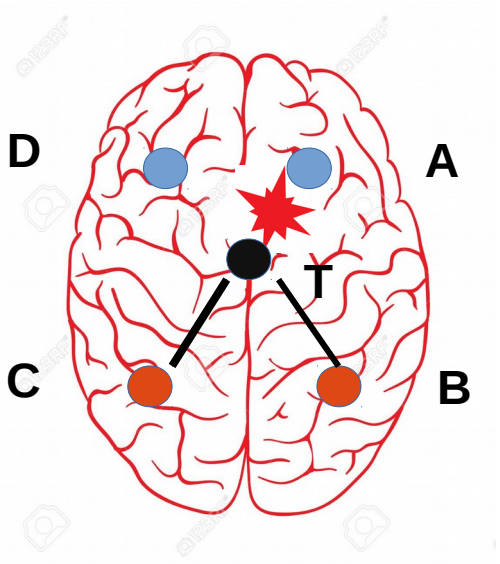
1) are anomalies of FC a direct effect or a network effect?

2) Is communication impairment (if any) symmetric or not?

3) How can we restore functional balance by stimulation?

What (else) could we learn by neuroimaging?

- **effects on inter-areal communication** [resting-state ***directed connectivity***]

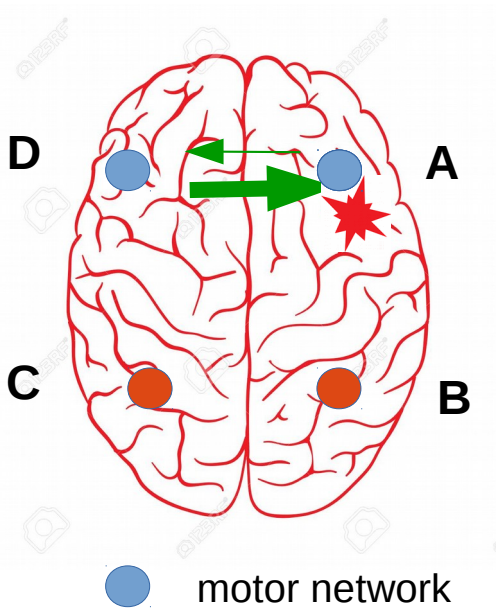


perhaps most effects come from indirect connections via subcortical structures such as thalamus...

Are anomalies of FC a direct effect or a network effect?

What (else) could we learn by neuroimaging?

- **effects on inter-areal communication** [resting-state ***directed connectivity***]



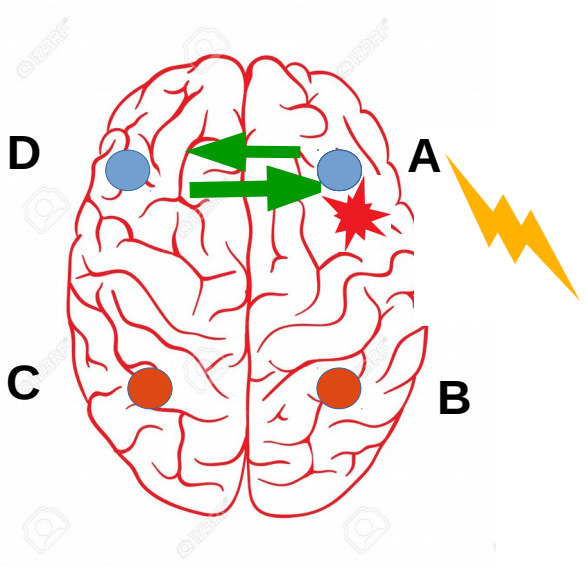
...As a consequence of asymmetries, some areas may overexcite/overinhibit others

...E.g. contralesional M1 can overinihbit ipsilesional M1

Is communication impairment (if any) symmetric or not?

What (else) could we learn by neuroimaging?

- **effects on inter-areal communication** [resting-state ***directed connectivity***]



...Perhaps we can restore balance by appropriately stimulating with TMS

How can we restore functional balance by stimulation?

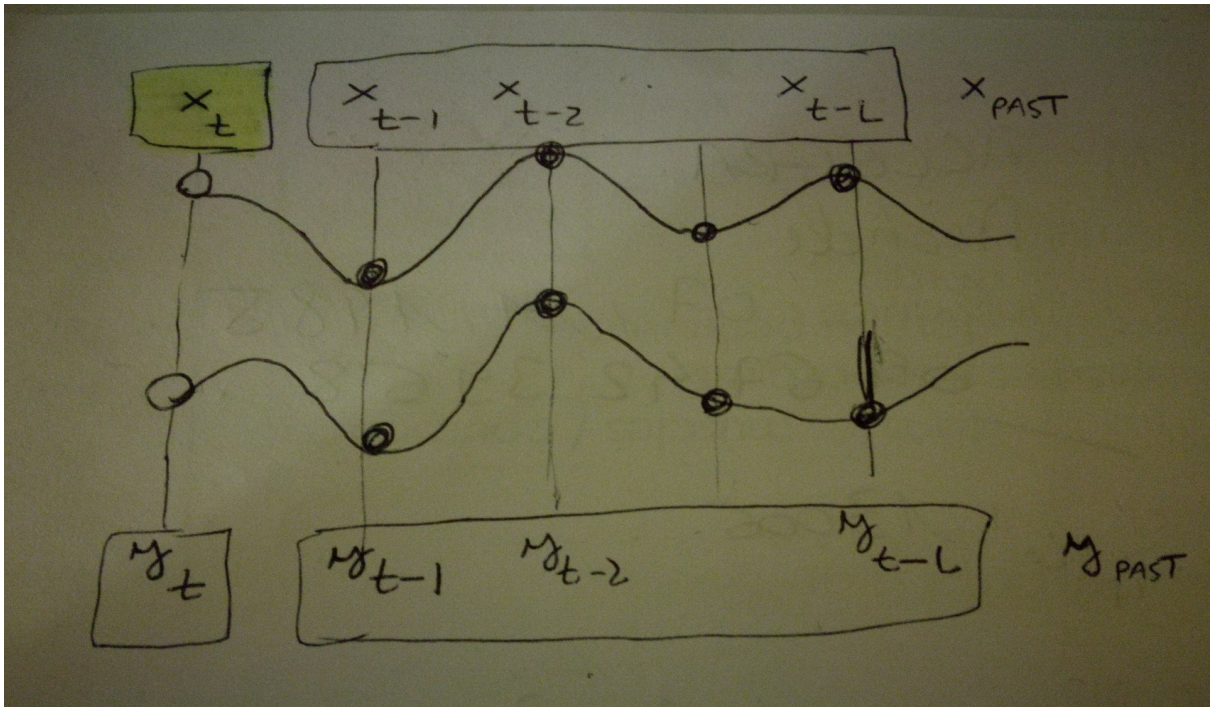
Inter-areal communication in stroke

Andrea Brovelli

Maurizio Corbetta

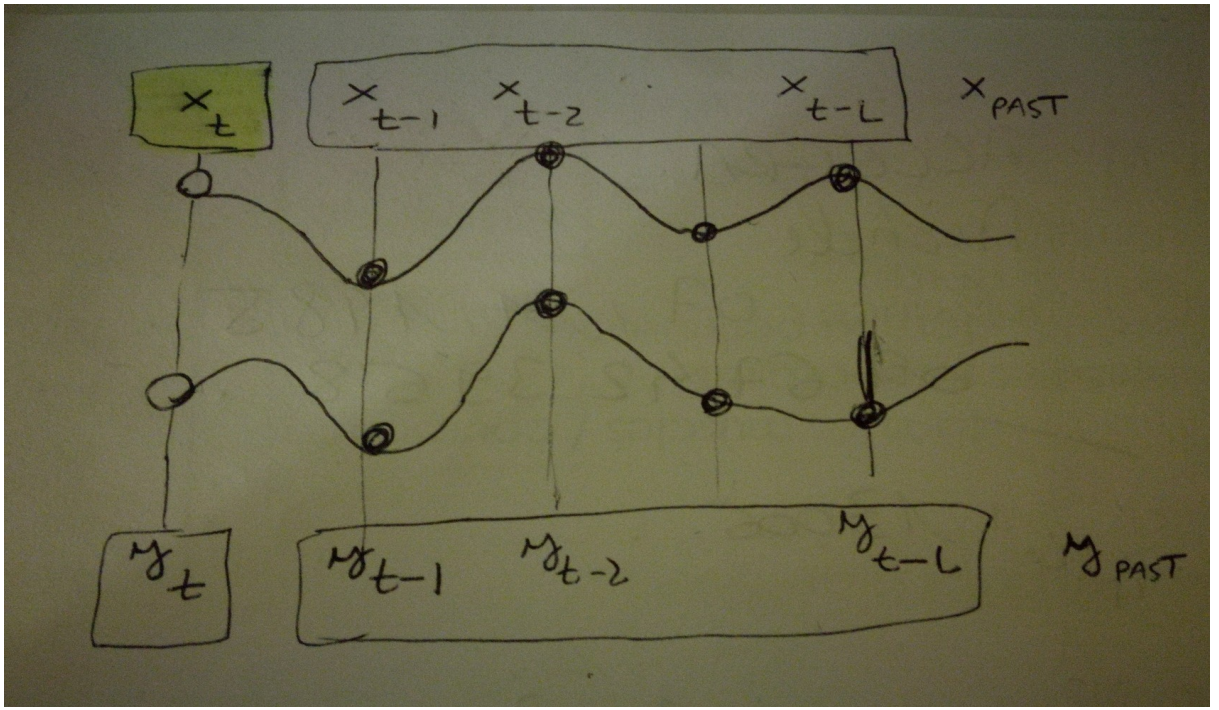
- Large (n>**100 patients**) stroke database from Washington University
- For each patient we **~30 mins resting state fMRI** acquired 2 weeks after stroke
- **We use covariance-based Granger Causality to study whole-brain inter-areal communication in stroke**
- M. Allegra, C. Favaretto, M. Corbetta, A.Brovelli, in prep. (2020)
  https://micheleallegra.github.io/

Covariance-based Granger causality



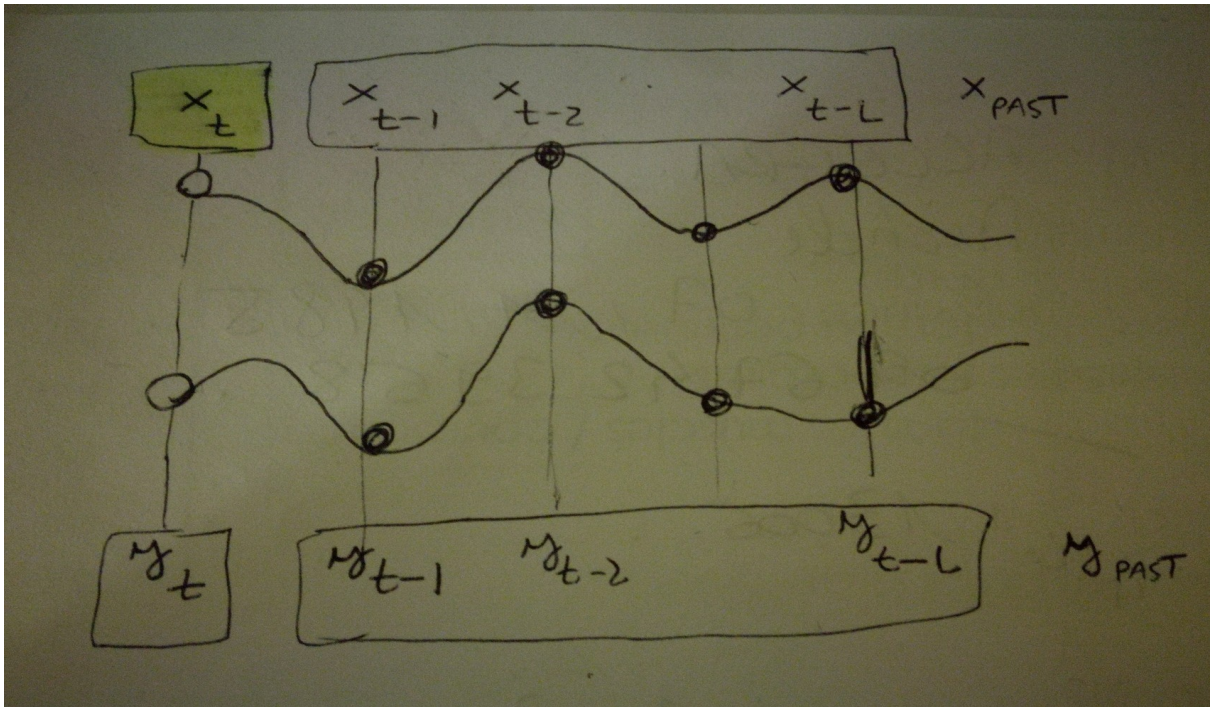
- uncertainty of x_t = $H(x_t)$ [H=Shannon entropy]
- uncertainty of x_t if x_{past} is known $H(x_t|x_{past})$
- **information about x_t contained in x_{past}**: $H(x_t) - H(x_t|x_{past})$

Covariance-based Granger causality



- information about x_t contained in x_{past}: $H(x_t) - H(x_t|x_{past})$
- information about x_t contained jointly in x_{past} and y_{past}: $H(x_t|x_{past}y_{past})$
- **information about X_t contained exclusively in Y_{past}**: $H(x_t|x_{past}) - H(x_t|x_{past}y_{past})$
- This is indicated by $F_{Y \rightarrow X}$

Covariance-based Granger causality



- information about x_t contained jointly in x_t, x_{past} and y_t: $H(x_t|x_{past}y_{past}y_t)$
- **information about x_t contained exclusively in y_t**: $H(x_t|x_{past}y_{past}) - H(x_t|x_{past}y_{past}y_t)$
- This is indicated by $F_{X \cdot Y}$

- **information about x_t contained exclusively in y_{past}**: (and not in x_{past}) :

$$F_{Y \to X} = H(x_t|x_{past}) - H(x_t|x_{past}y_{past})$$

- **information about x_t contained exclusively in y_t** (and not in $x_{past}y_{past}$) :

$$F_{Y \to X} = H(x_t|x_{past}y_{past}) - H(x_t|x_{past}y_{past}y_t)$$

- $F_{X \to Y}$ (or $F_{Y \to X}$) was called ***transfer entropy*** by Shreiber [T. Schreiber, Phys. Rev. Lett. 85, 461, 2001)]

  directed information flow from X to Y (or Y to X)

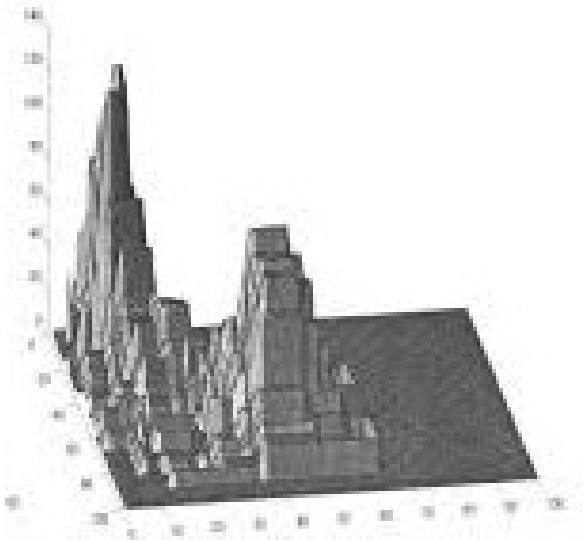
- $F_{X \cdot Y}$ was called ***instantaneous feedback*** by Geweke [J. Geweke, J. Am. Stat. Ass. 77.378 (1982)]

  «instantaneous» ($\Delta t<1$) information flow/sharing between X and Y

- $F_{X \to Y}$ $F_{Y \to X}$ coincide with notion of ***Granger causality*** for Gaussian systems
  [L. Barnett et al., Phys. Rev. Lett. 103, 238701 (2009)]

Covariance-based Granger causality

- **estimate $F_{X \to Y}$, $F_{Y \to X}$, and $F_{X \cdot Y}$** :
- **need to compute Shannon entropies** from $P(x_t y_t x_{past} y_{past})$ and its marginals
- **binning method**: approximate $P(x_t y_t x_{past} y_{past})$ with multidimensional histogram:
- $\mathbf{B^{2(L+1)}}$ bins needed!
- **Problem:** fMRI time series are short, not enough points for estimation!

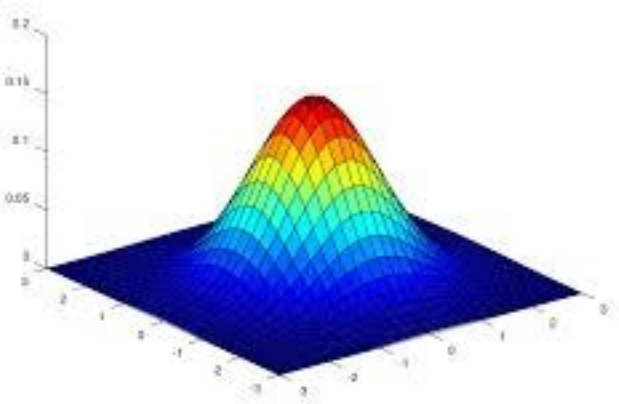


Covariance-based Granger causality

- **assume multivariate Gaussian**, P=N(μ,Σ) [Σ=covariance matrix]

  H = 1/2 log(det(Σ)) + const.

  all entropies can be computed from Σ and its submatrices, only $4(L+1)^2$ parameters!

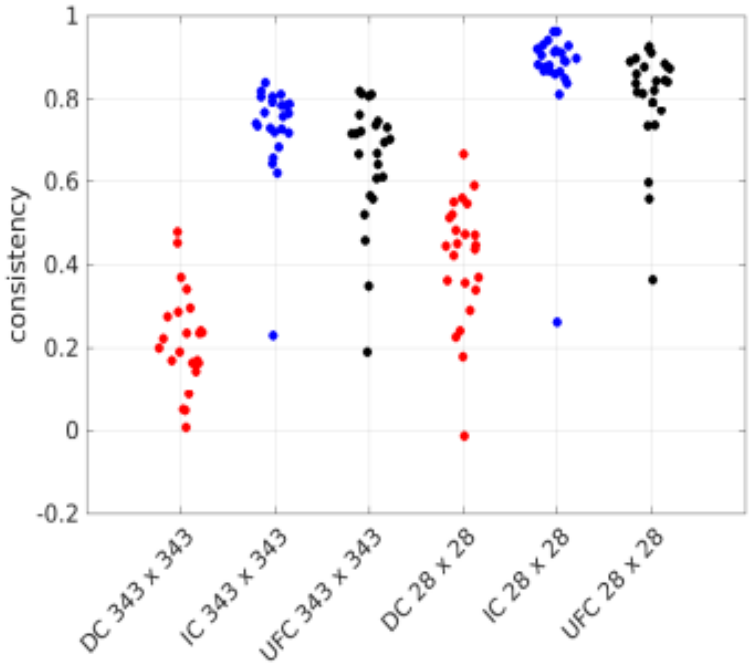


- ***covariance-based* Granger causality measures**
  A. Brovelli et al., J. Neuro. 35(37) (2015)

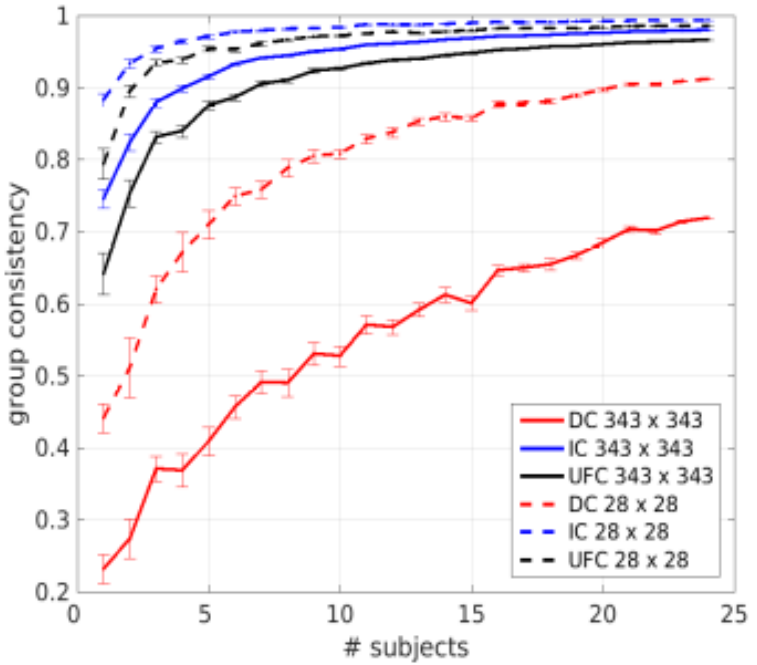
- $F_{X \cdot Y}$: Instantaneous Causality, **IC**
- $F_{X \to Y}$, $F_{Y \to X}$: Directed Causality, **DC**

Covariance-based Granger causality and fMRI stroke data

- Compute GC, IC on 324 regions from cortical atlas (Gordonn-Laumann)
- **Does it work? Check methodological consistency**



(a)



(b)

Individual results of IC are robust, especially if one averages over many regions

Covariance-based Granger causality and fMRI stroke data

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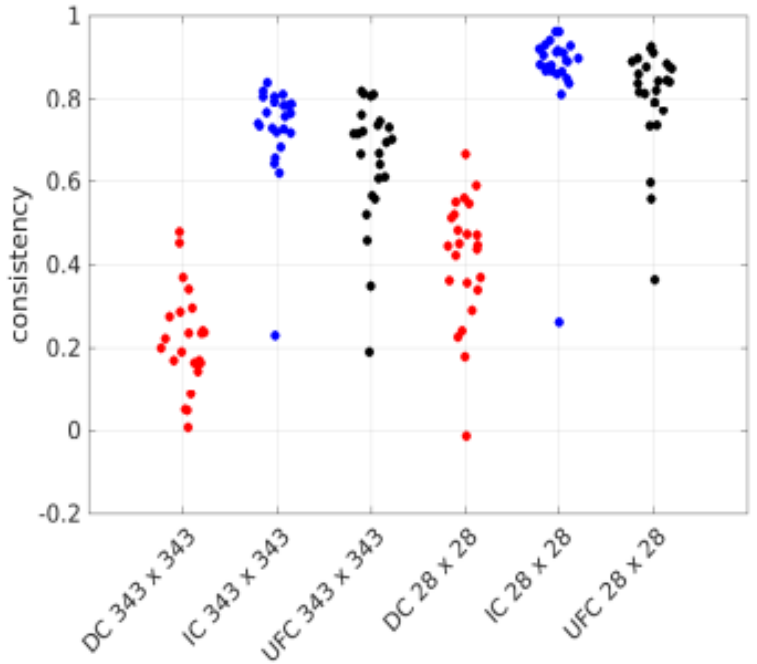

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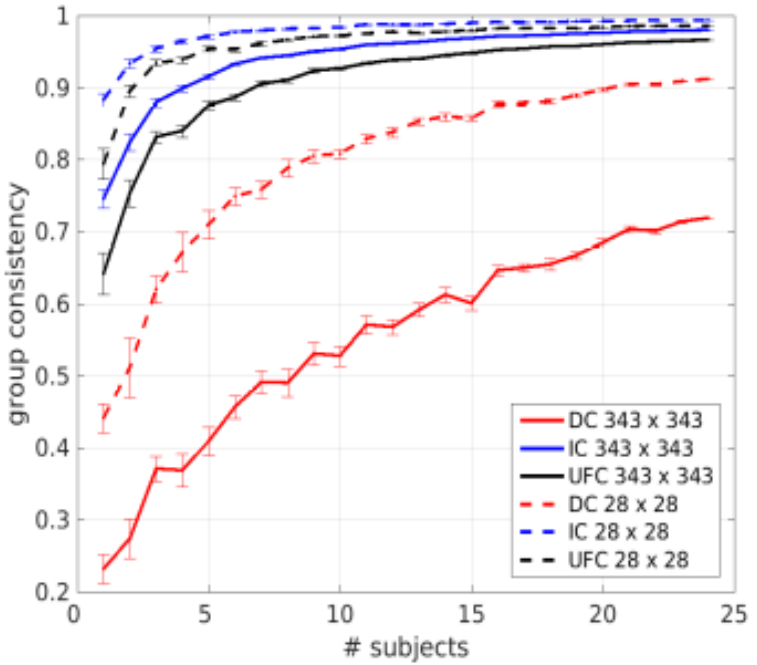
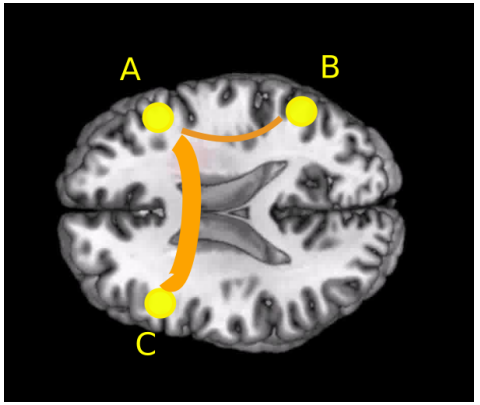


(b)

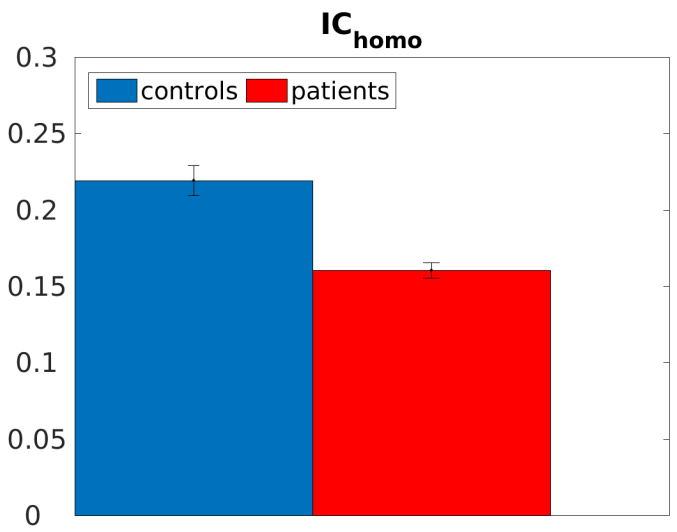
Individual results of GC are not robust, even taking averages over many regions

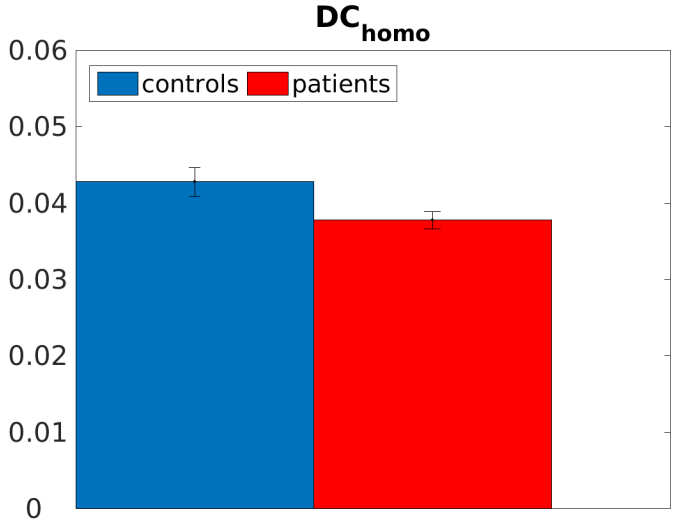
group results are robust

Information transfer in the brain upon stroke



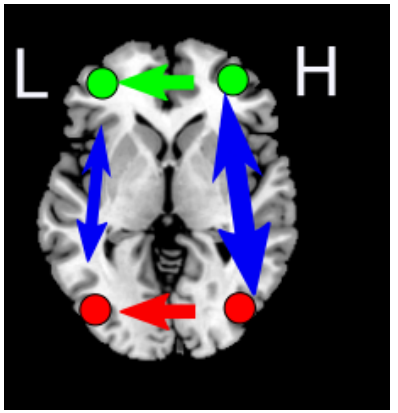
- **Homotopic information transfer**



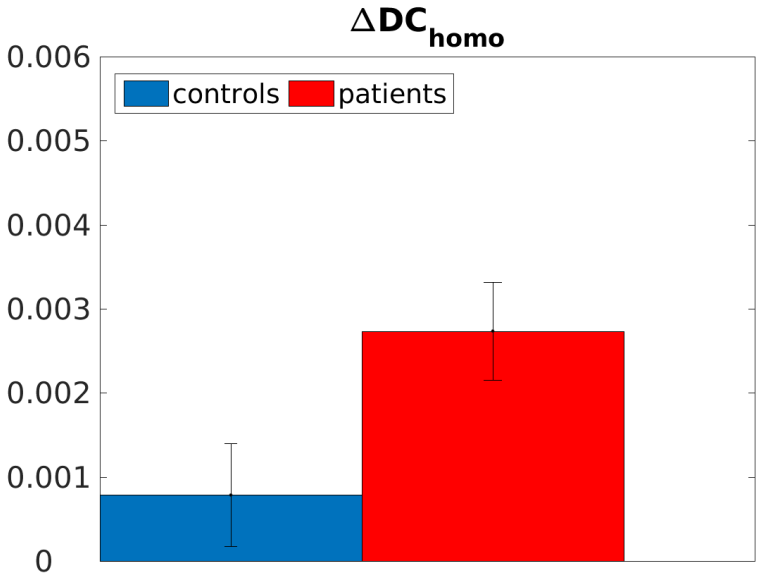


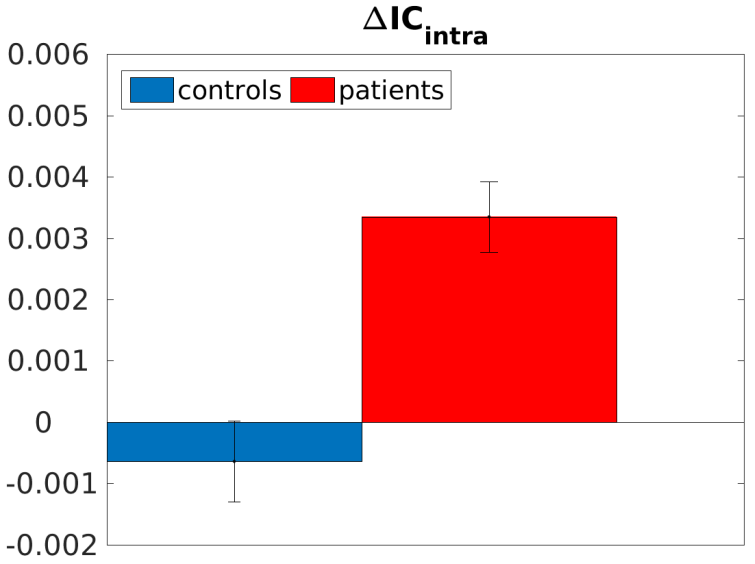
- Instantaneous Causality for homologous regions (IC_{homo}): reduced in patients
- Directed Causality for homologous regions (DC_{homo}): reduced in patients
- **Interhemispheric communication (IC and DC) is reduced in patients**

Information transfer in the brain upon stroke



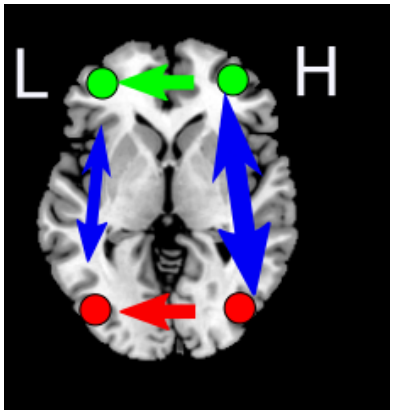
- **Imbalances between healthy and lesioned hemisphere**



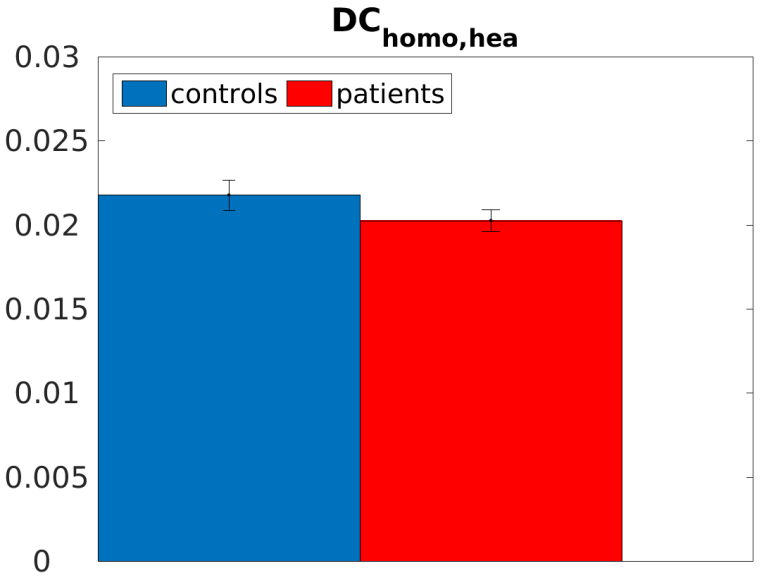


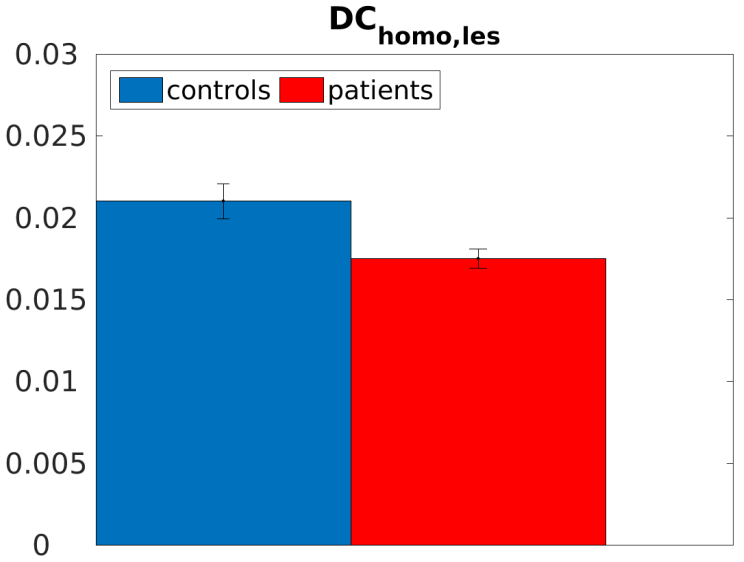
- Net direction of homotopic DC (healthy to lesioned - lesioned to healthy) : ΔDC_{homo}
  DC from healthy to lesioned hemisphere higher than reverse in patients
- IC for regions of same hemisphere, then difference healthy – lesioned (ΔIC_{intra}):
  intra-hemispheric IC higher in the healthy hemisphere for patients […similar effect for DC]
- **Communication within and from the lesioned hemisphere is reduced**

Information transfer in the brain upon stroke



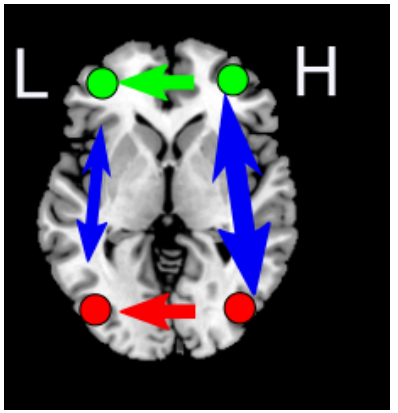
What is the origin of the imbalance?



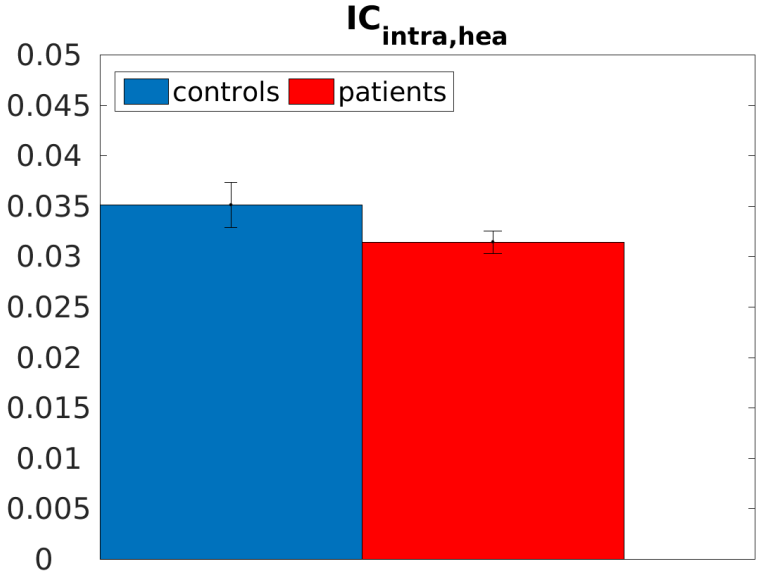


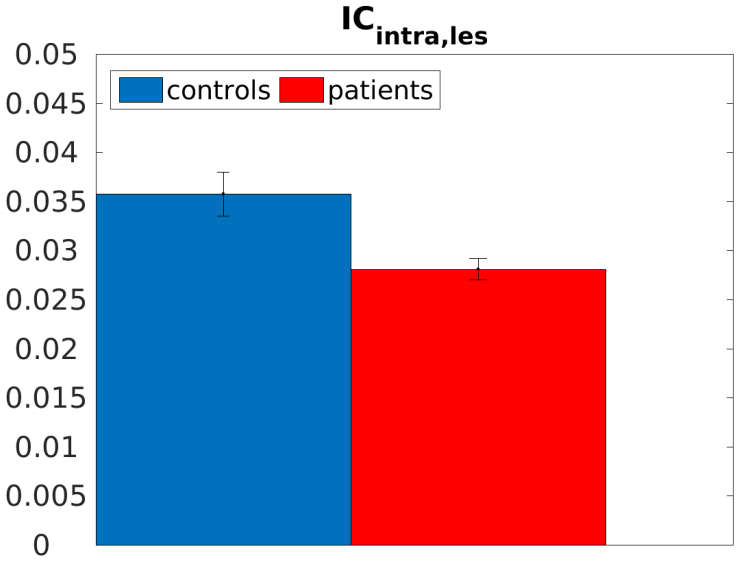
The homotopic FC from lesioned to healthy hemisphere is reduced in patients

Information transfer in the brain upon stroke



- **What is the origin of the imbalance?**





The intrahemispheric IC in lesioned hemisphere is reduced in patients

Information flow from and within the lesioned hemisphere is reduced

Stroke signatures

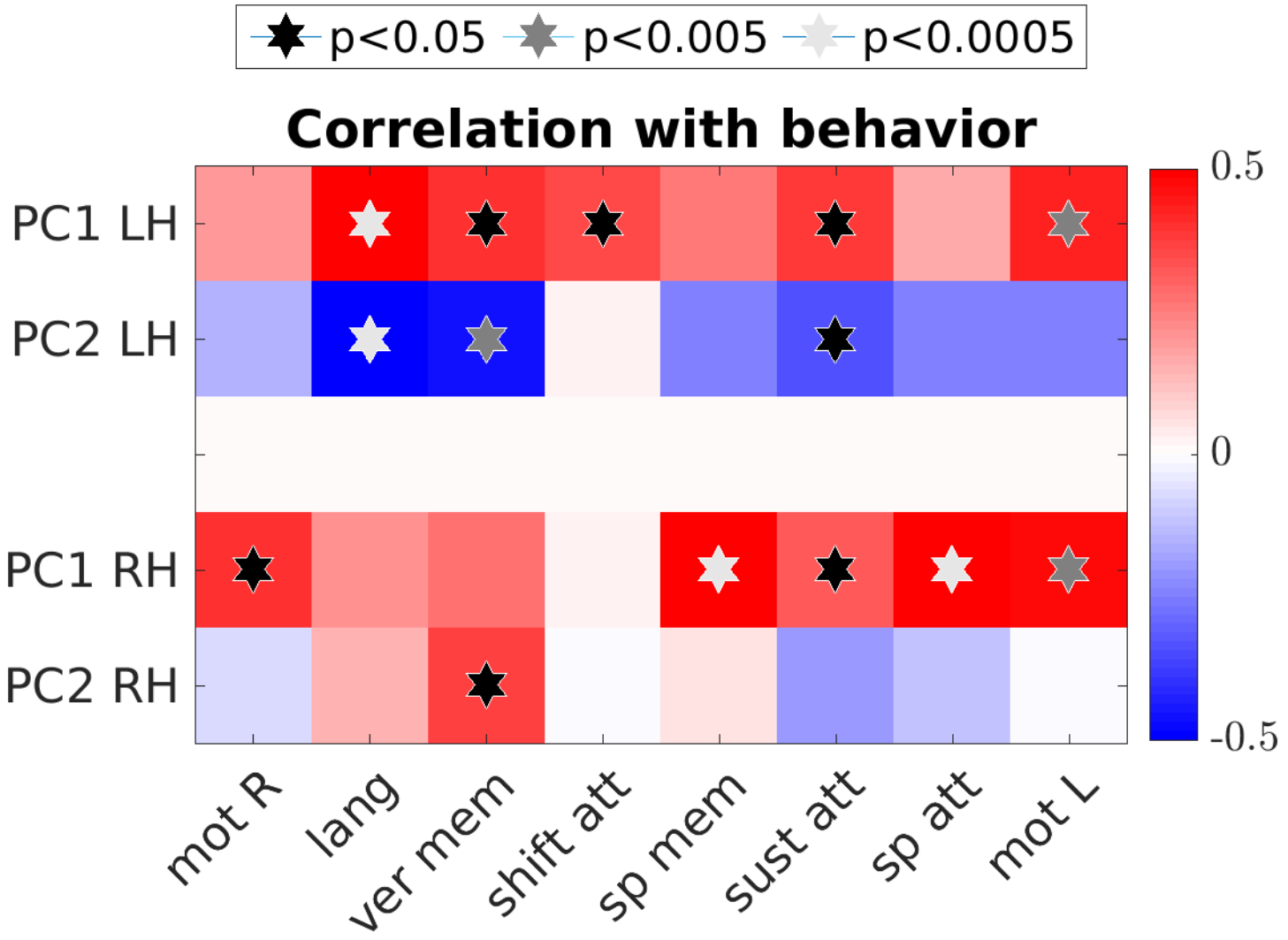
We obtain functional bio-markers of stroke:

- IC_{homo} (average homotopic instantaneous causality)
- DC_{homo} (average homotopic directed causality)
- ΔDC_{homo} (lesioned/healthy asymmetry in homotopic directed causality)
- ΔIC_{intra} (average intrahemispheric functional connectivity)
- ΔDC_{intra} (lesione/healthy asymmetry in intra-hemispheric instantaneous causality)

- By doing a PCA on the markers [across patients] we find two components: **PC1** and **PC2**

- **PC1 loads on omotopic measures IC_{homo} , DC_{homo} that are reduced in patients**
- **PC2 load on «unbalance» measures ΔDC_{homo}, ΔIC_{intra} , ΔDC_{intra} that are enhanced in patients**

Relation with behavior

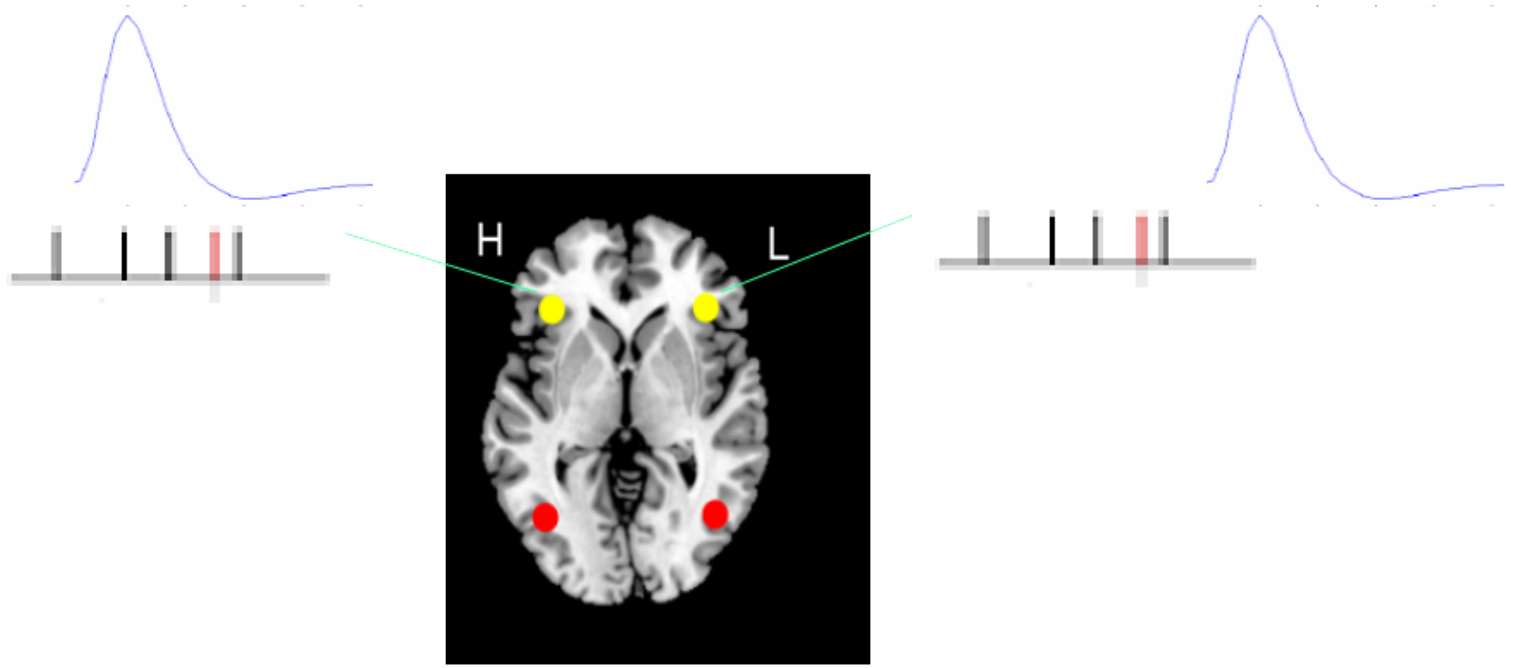


Behavioral effects are different for LH and RH patients, which agrees with expectation

Check: effect of hemodynamics?

Observed imbalance in information transfer can be due to spurious influence of hemodynamics

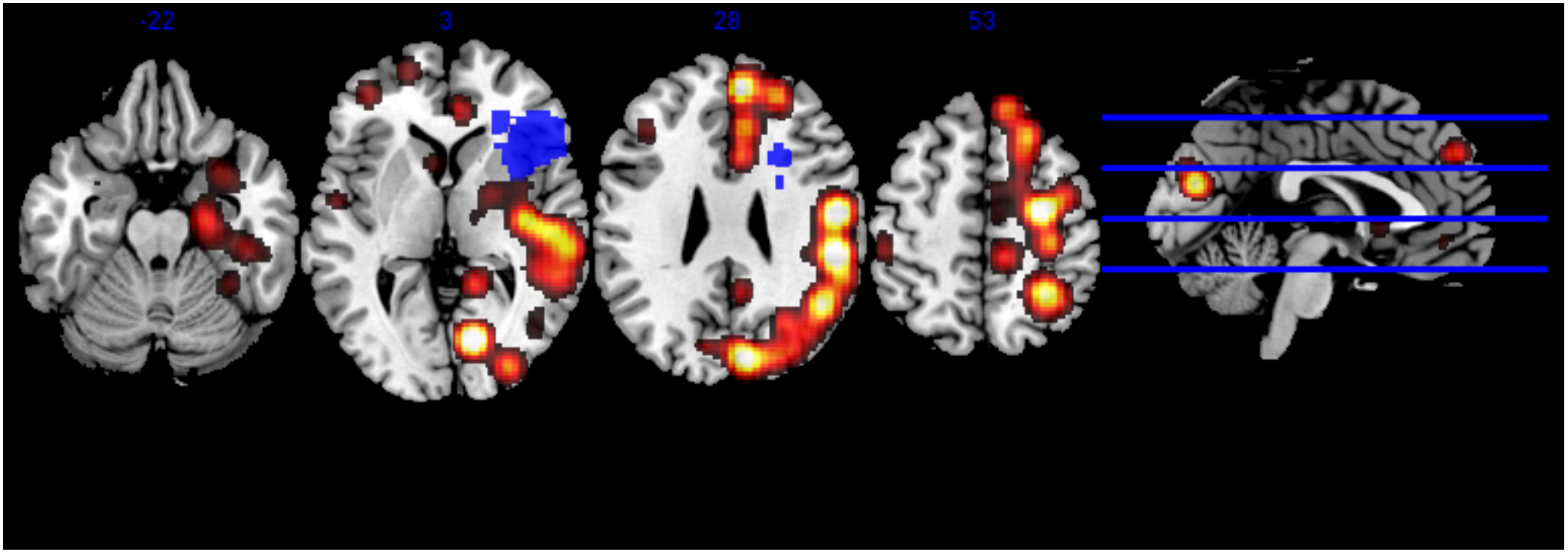
hemodynamic response in lesioned hemisphere can be anomalously retarded



Check: effect of hemodynamics?

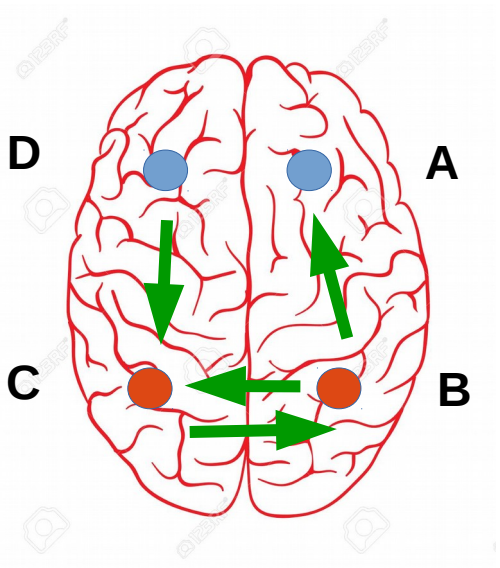
Observed imbalance in information transfer can be due to spurious influence of hemodynamics

However, GC asymmetries are found very far from lesion



What (else) could we learn by neuroimaging?

3) effects on inter-areal communication [*directed connectivity*]



1) are anomalies of FC a direct effect or a network effect?

The IC results suggest important mediation effect of e.g. subcortical structures

2) Is communication impairment (if any) symmetric or not?

Stroke creates strong asymmetries in information flow

3) How can we restore functional balance by stimulation?

For this we need more reliable measures of directed connectivity at level of singe subject, single area

Conclusions

- Our goal was to characterize individual anomalies in inter-areal communication in stroke patients
- To this aim, we used resting-state fMRI and whole-brain covariance-based Granger Causality estimation
- While we cannot obtain robust estimates inf interareal communication for individual patients and single brain regions, we obtain solid individual results for network-wise measures of information transefer
- In particular, we define stroke global markes summarizing inter- and intra-hemispheric communication
- The «disconnection» between hemispheres in stroke can be traced back to a reduction of The inter-hemispheric communcation; part of the communication likely occurs thorugh indirect pathways (e.g. subcortical structures)
- Stroke determines a global inbalance between the hemispehres, as communication within and from the lesioned hemisphere is reduced in patients
- Both effects are of behavioral import

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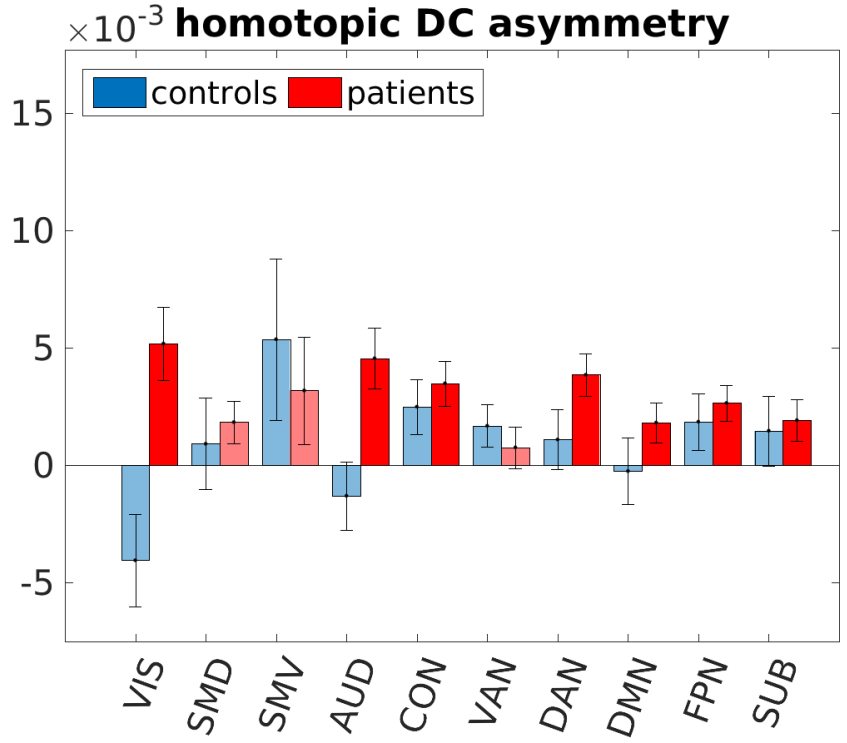
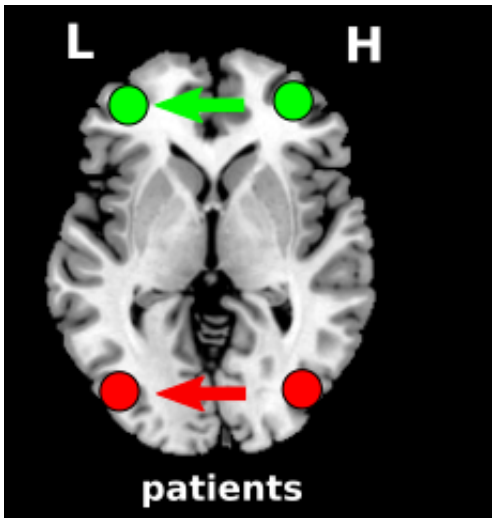
Thank you for your invitation and attention!

Homotopic DC Asymmetry

The effect is more pronounced in VIS,AUD,CON,DAN,FPN and subcortical regions





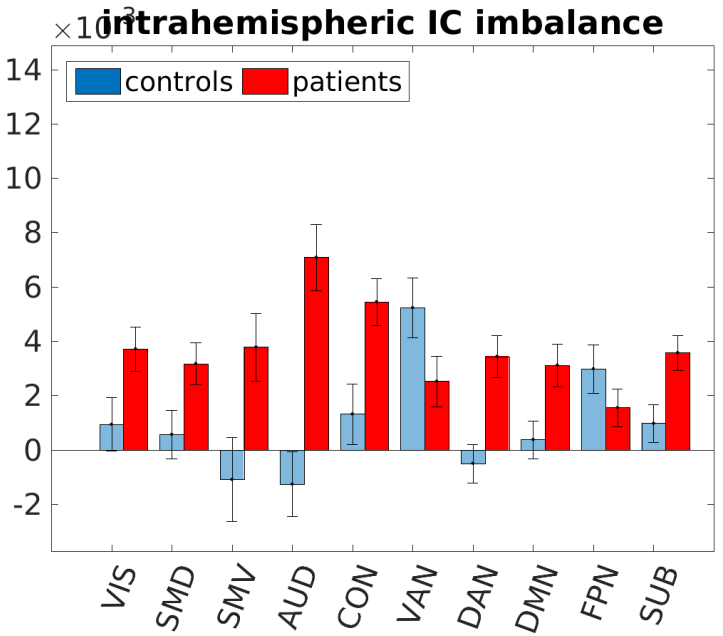
The interhemispheric (homotopic) DC from the healthy to the lesioned hemisphere is higher than the reverse in patients

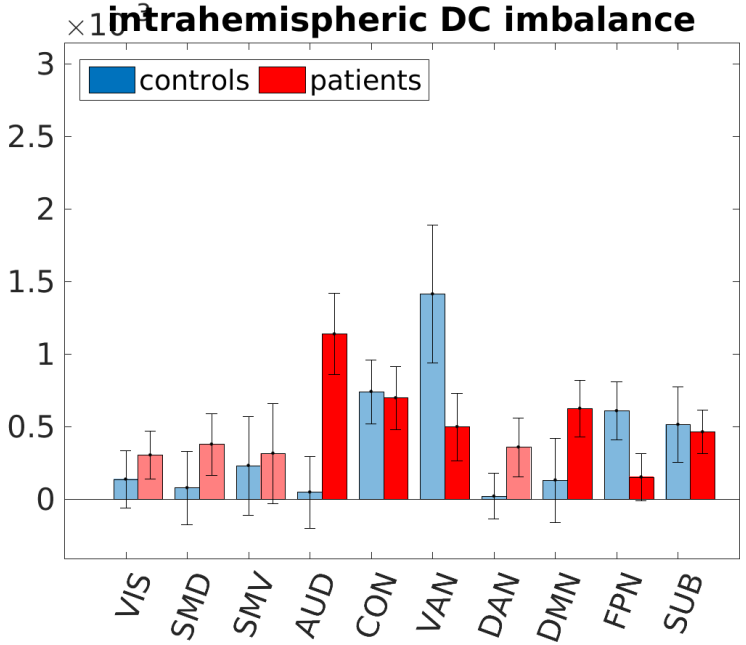
The net information flow is in the direction of the lesioned hemisphere

Intra-hemispheric GC

The effect is more pronounced in AUD,CON,DAN,DMN

AUD
CON
DAN





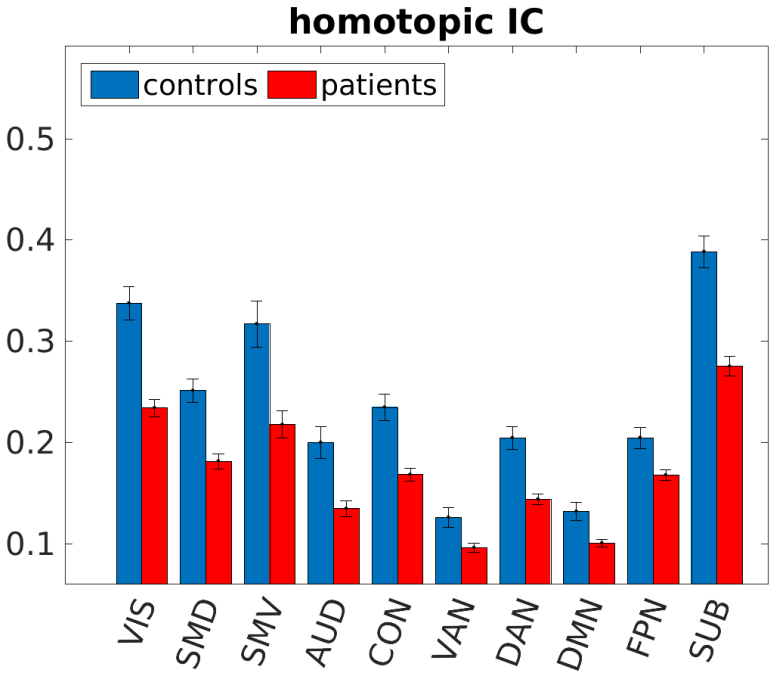
AUD
CON
DMN
sub

The intra-hemispheric IC is higher in the healthy hemisphere for patients

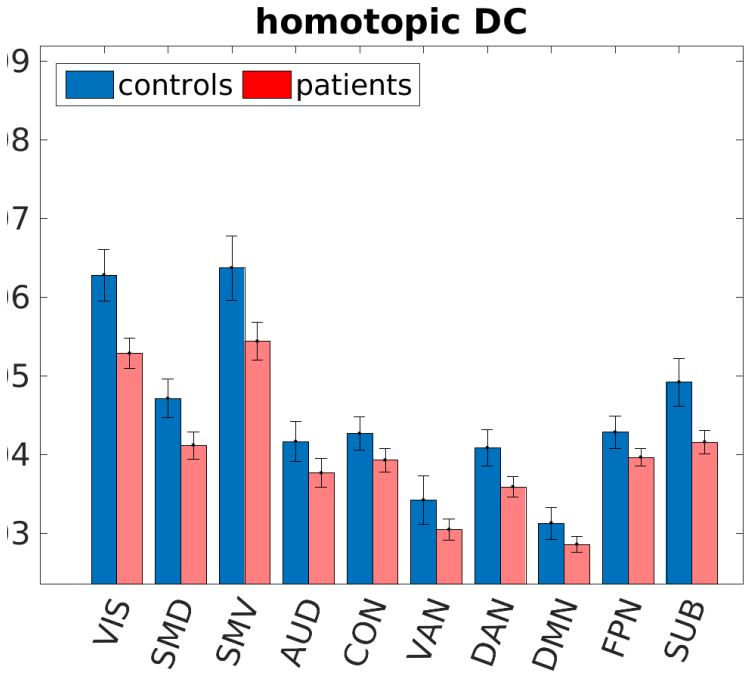
The intra-hemispheric DC is higher in the healthy hemisphere cor patients

Homotopic GC

The effect is more pronounced in some networks (networks for language, attention and motion)



Interhemispheric (homotopic) IC is reduced in patients



Interhemispheric (homotopic) DC is reduced in (LH) patients