MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

MASSACHUSETTS GENERAL HOSPITAL

Harvard-MIT Health Sciences & Technology

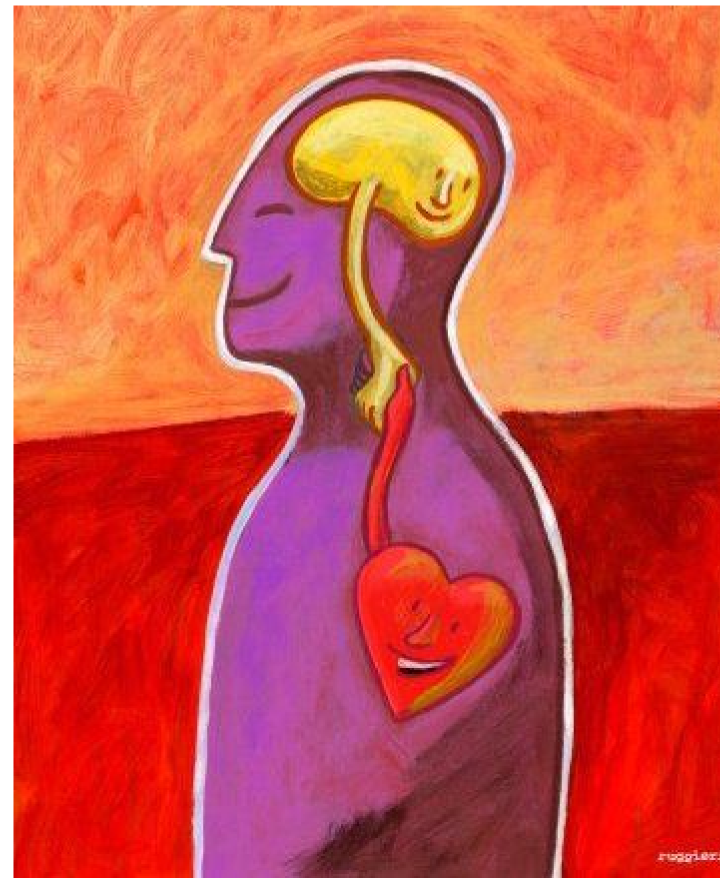
Università di Roma Tor Vergata

Globally conditioned causality in estimating directed brain-heart interactions through joint MRI and RR series analysis

Andrea Duggento[1], Marta Bianciardi[2], Lawrence L. Wald[2], Luca Passamonti[3], Maria Guerrisi[1], Riccardo Barbieri[4,5], Nicola Toschi[1,2]

1. Medical Physics Section, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome.
2. Department of Radiology, A.A. Martinos Center for Biomedical Imaging, MGH and Harvard Medical School, Boston,USA
3. Institute of Bioimaging and Molecular Physiology, National Research Council, Catanzaro, Italy
4. Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, MA, USA
5. Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, MA, USA

Brain correlates with autonomic system



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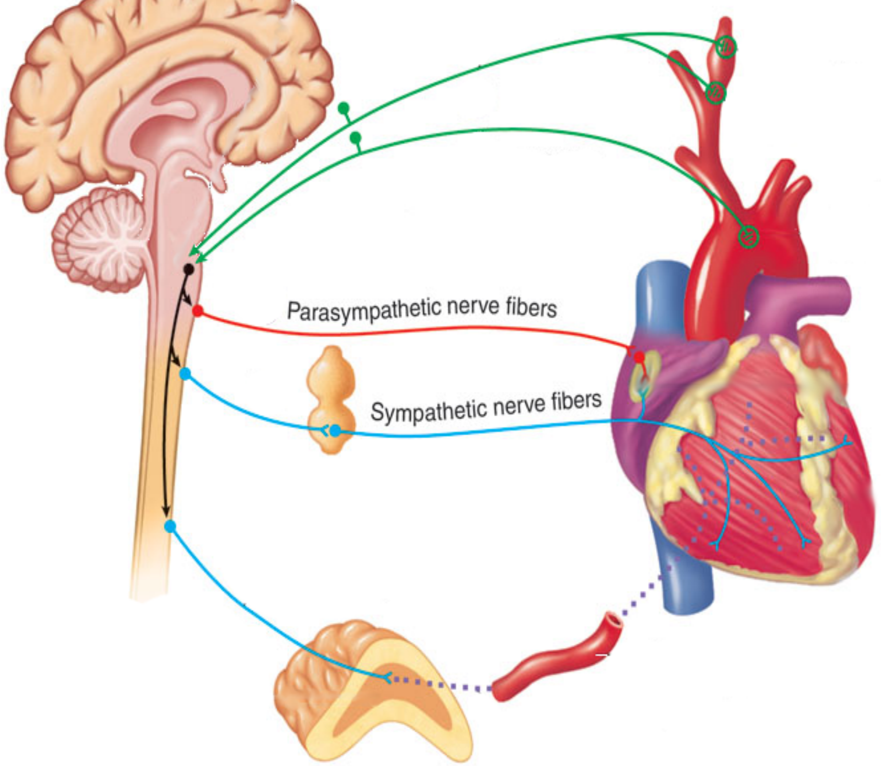
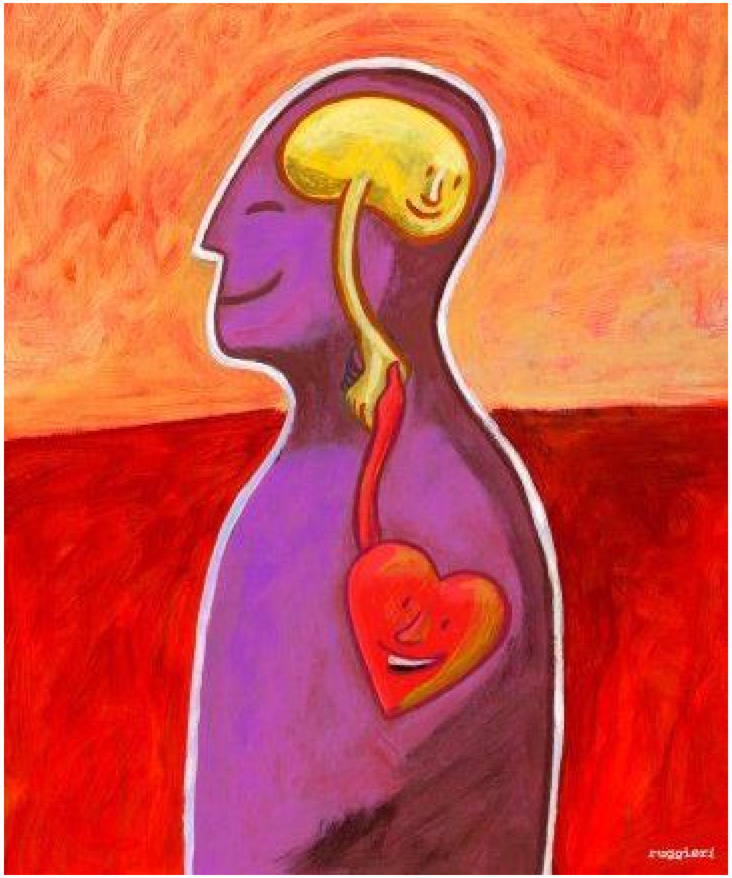
Is the "Autonomic" autonomous?





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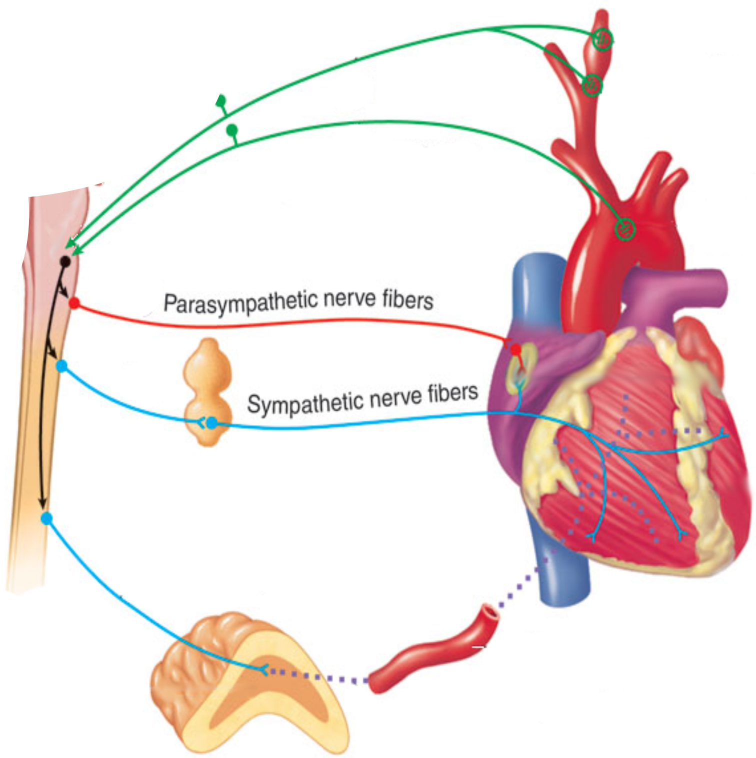

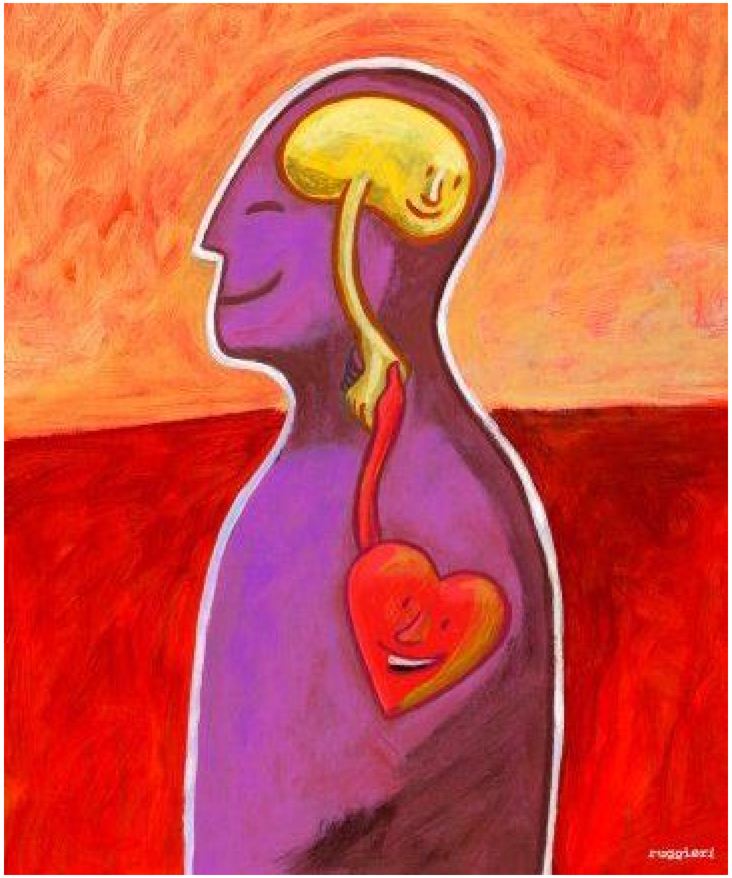

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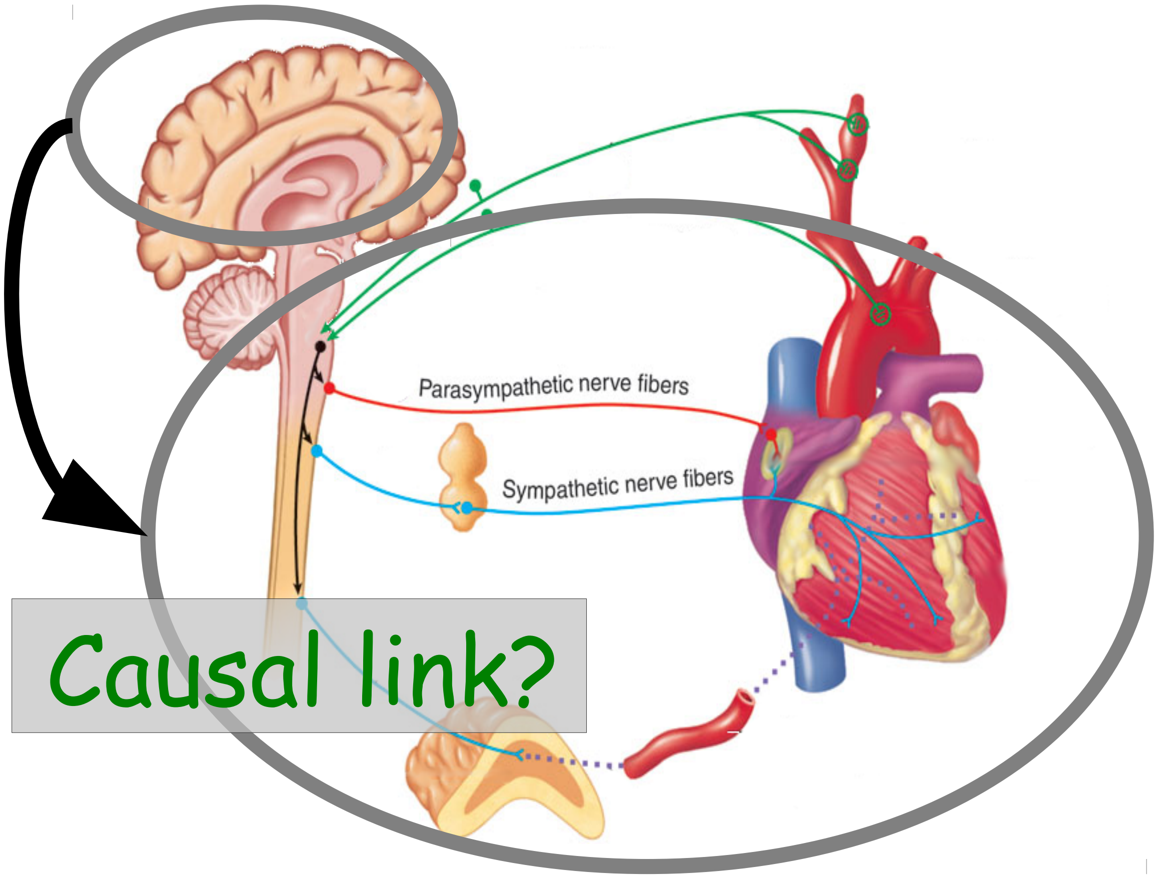
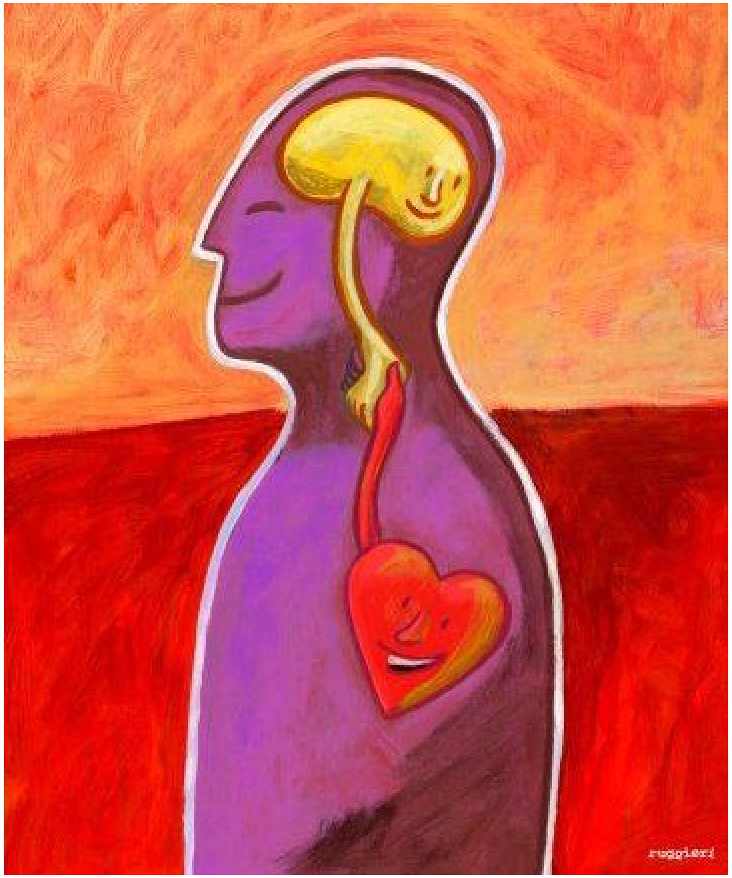
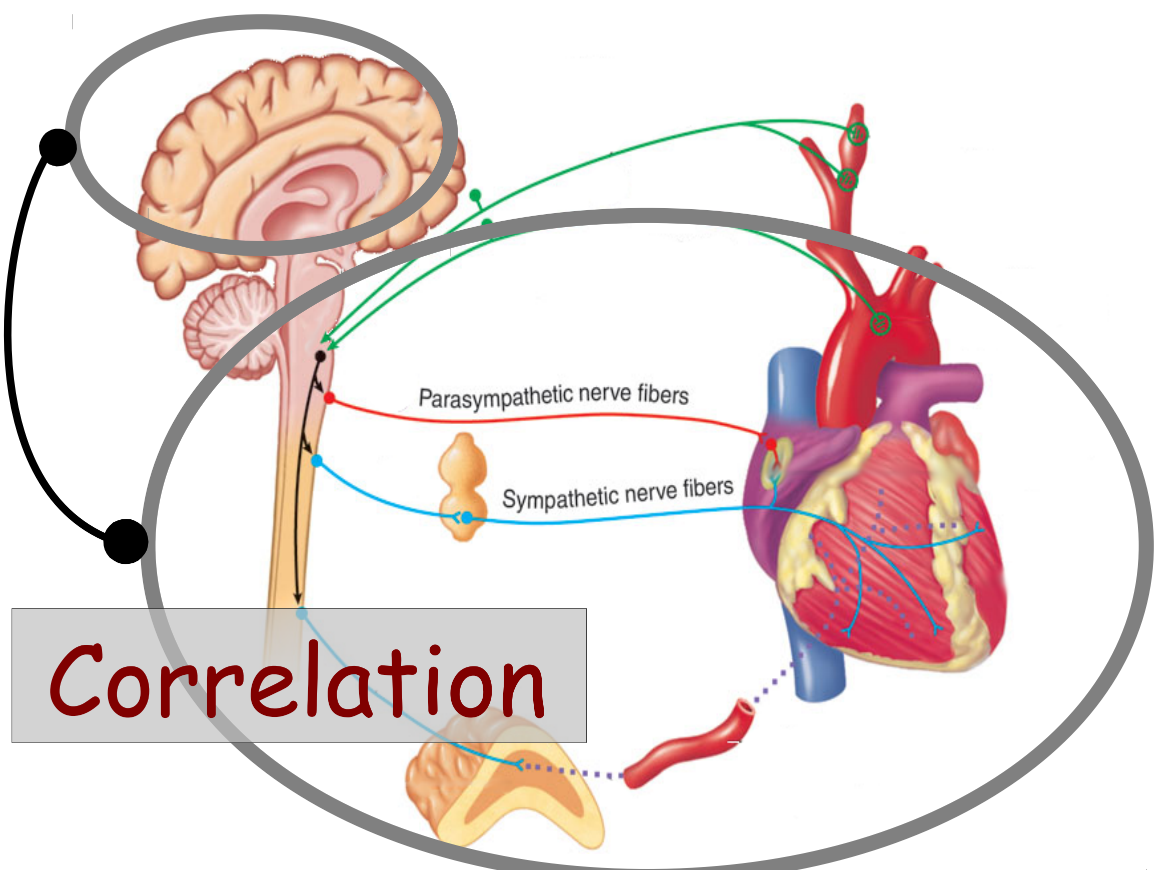


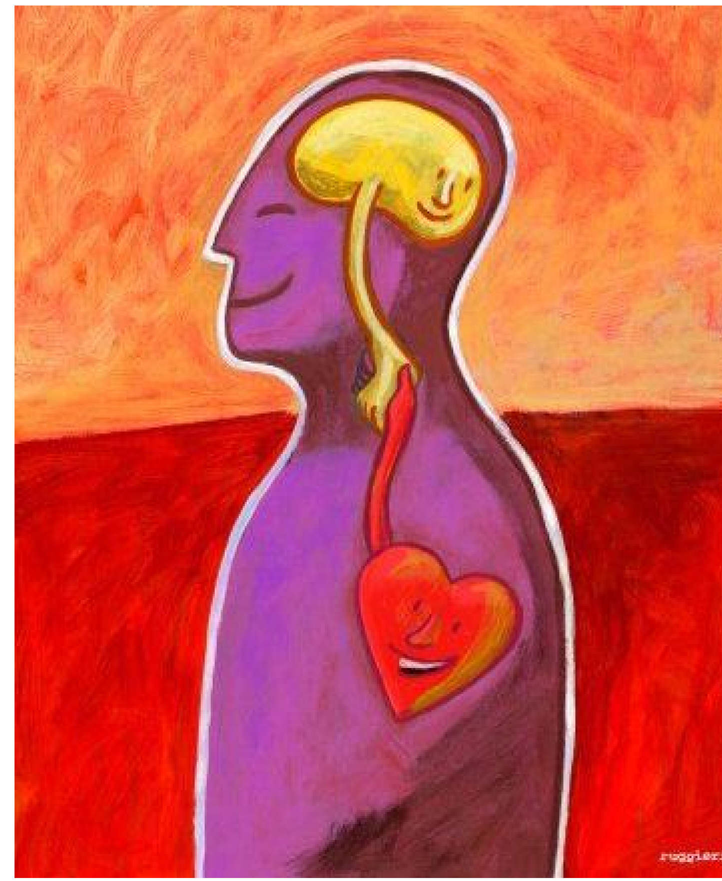


Brain correlates with autonomic system

Brain correlates of autonomic modulation: Combining heart rate variability with fMRI

Vitaly Napadow,[a,b,*] Rupali Dhond,[a,b] Giulia Conti,[c,d,e] Nikos Makris,[f]
Emery N. Brown,[c,d] and Riccardo Barbieri[c,d]





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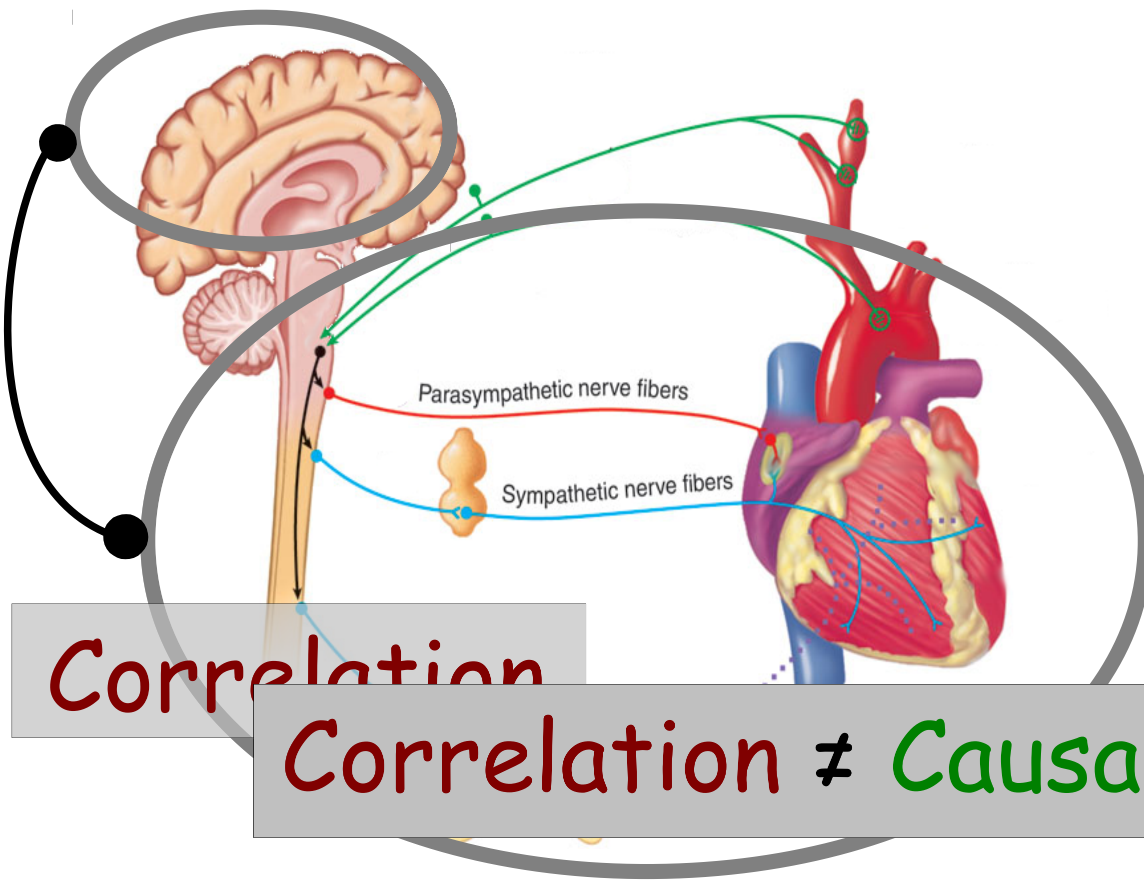
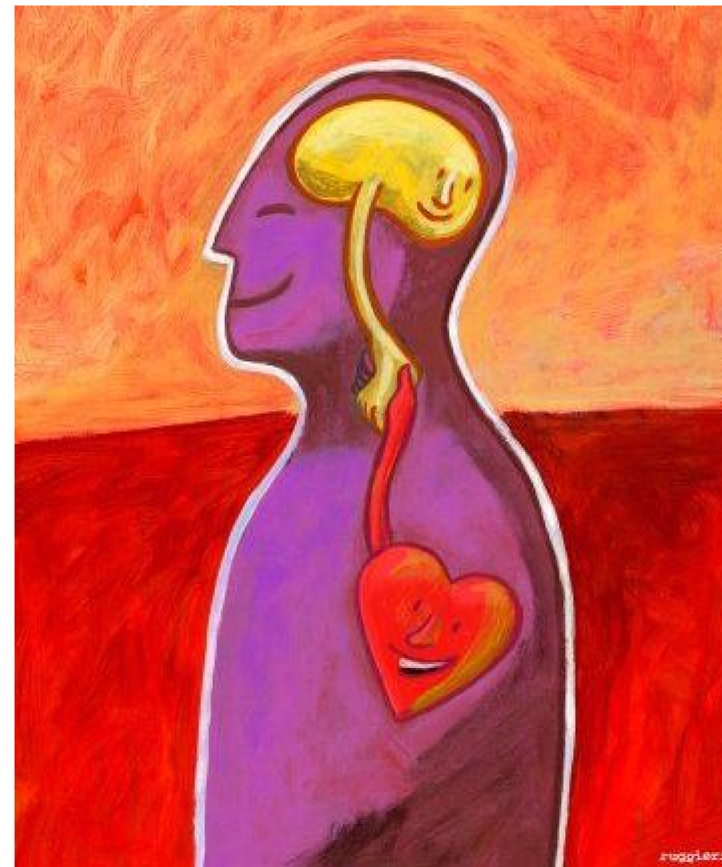


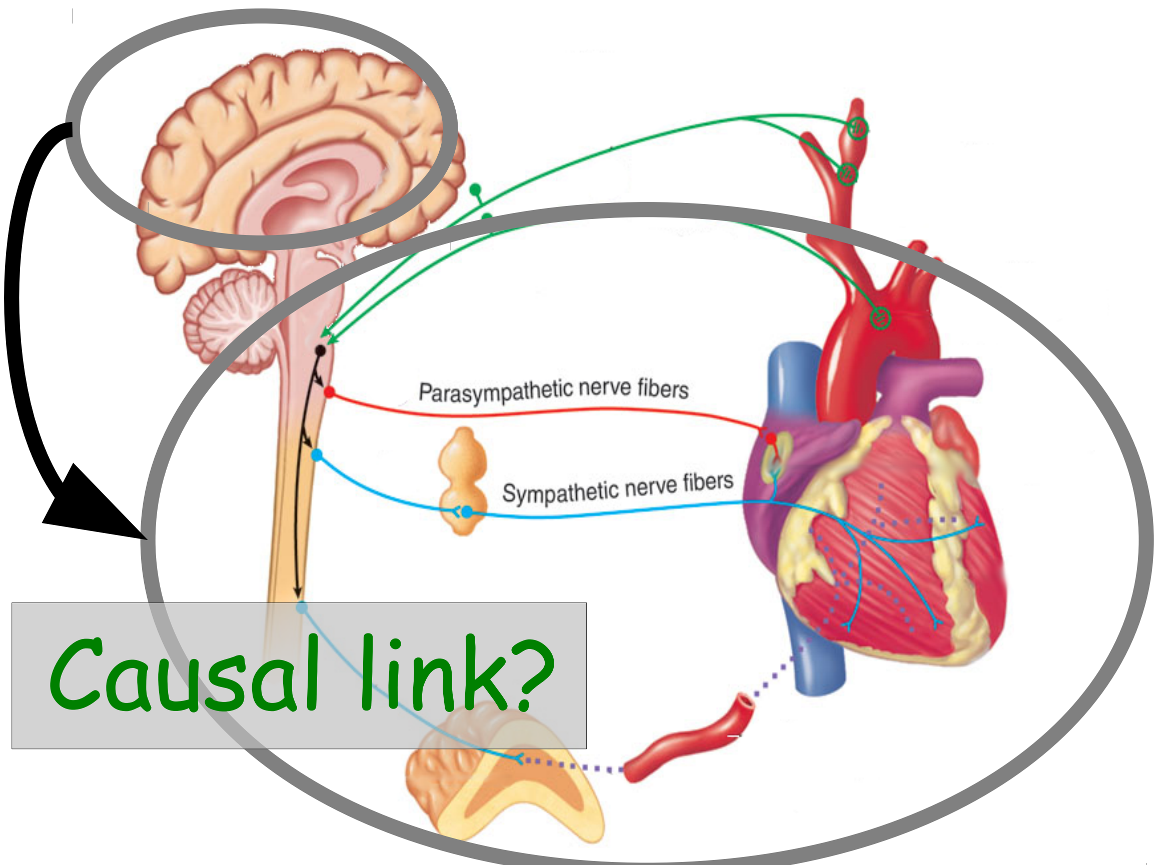


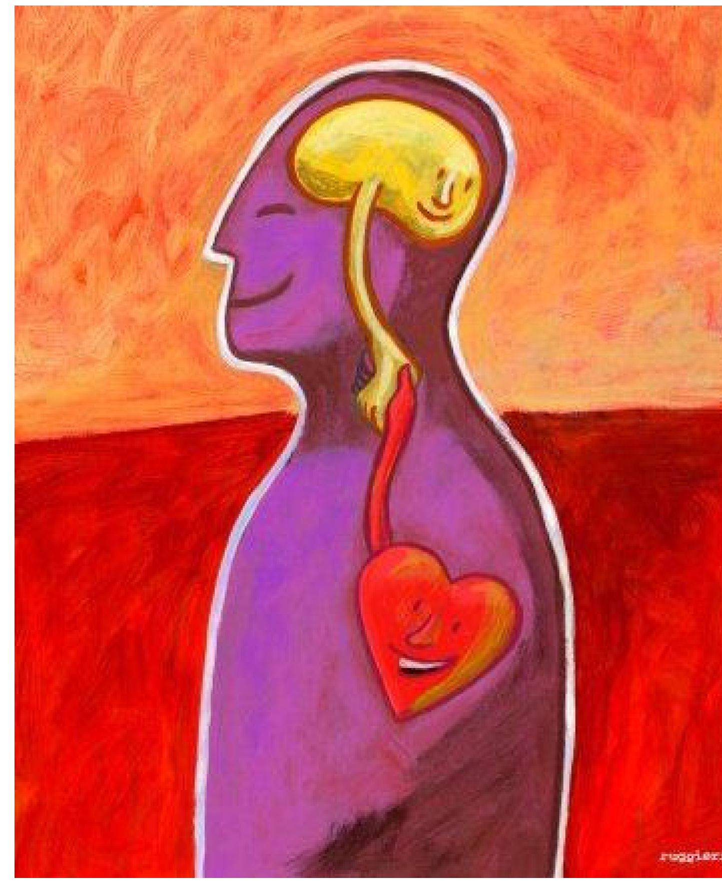
Correlation

Correlation ≠ Causation

Brain correlates with autonomic system

Causality is challenging:





Challenges in fMRI→ANS causality

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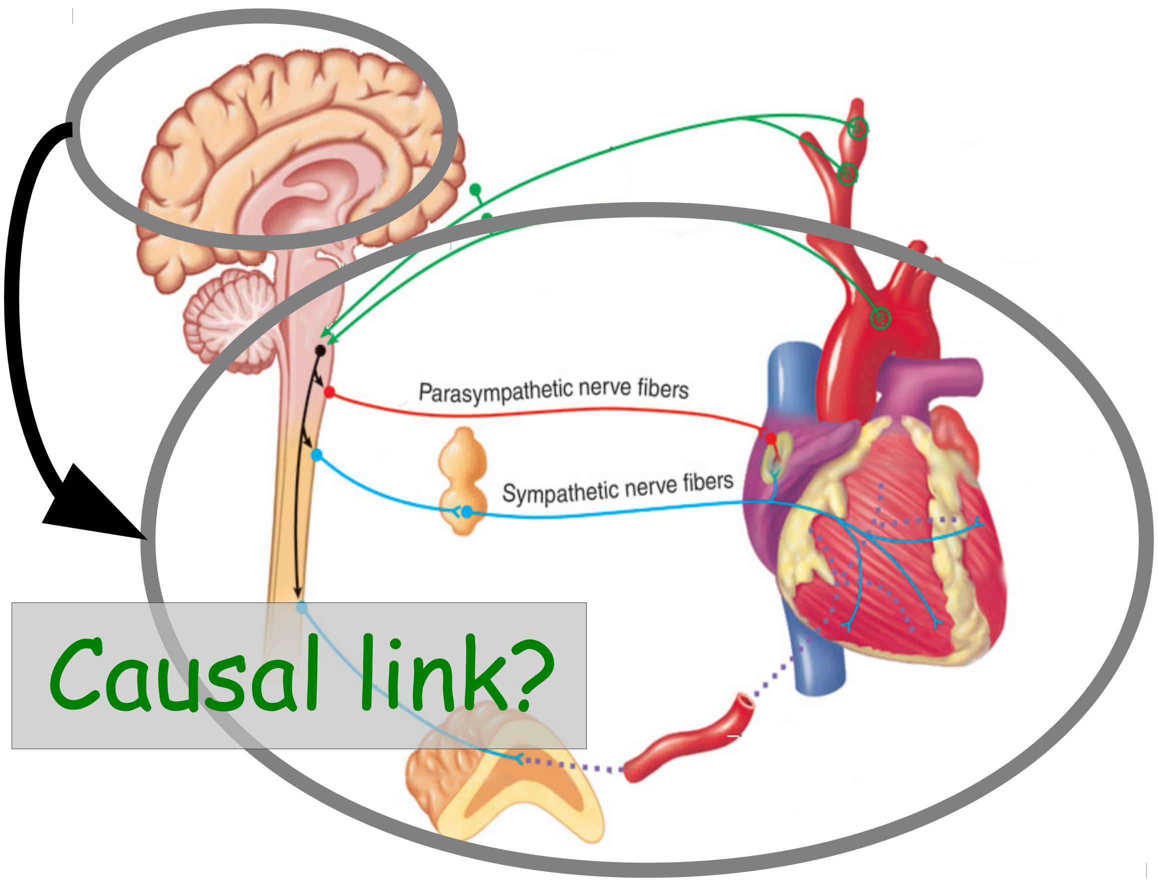

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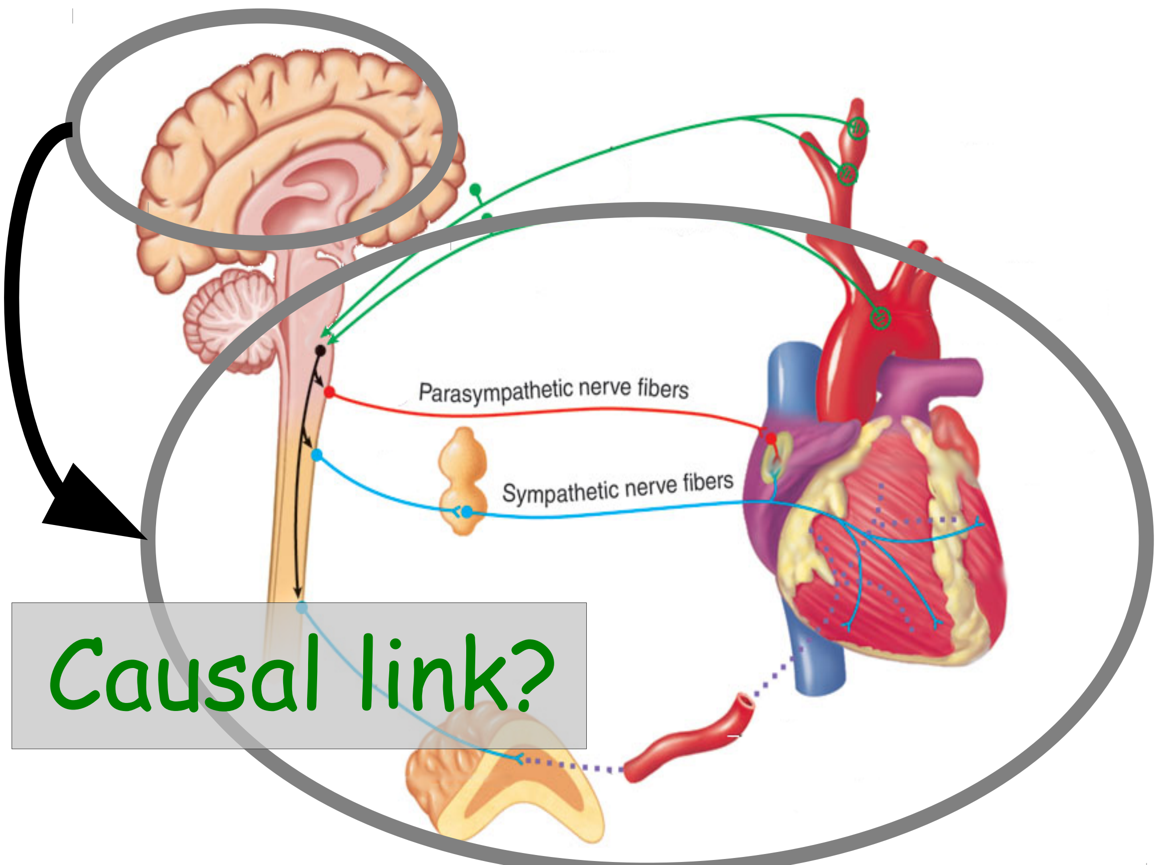

- SNR in fMRI, time-resolution

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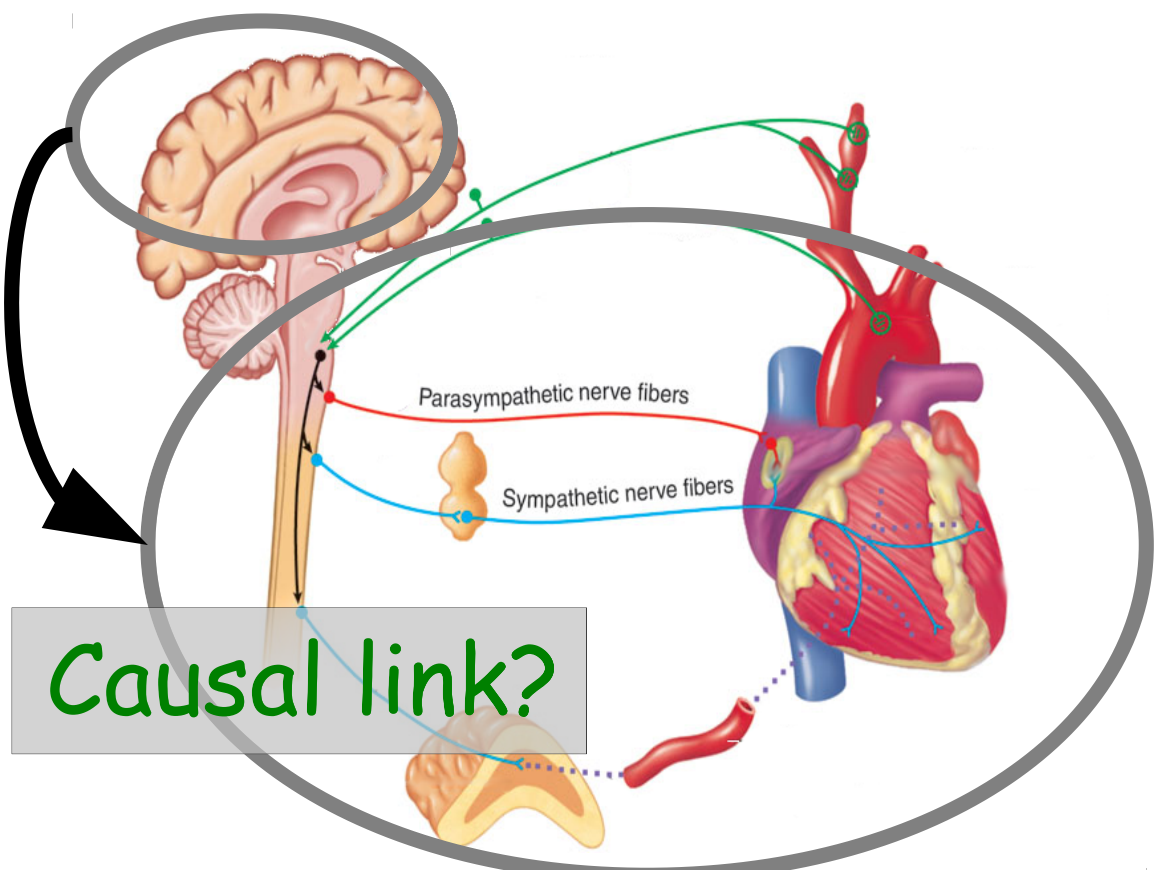

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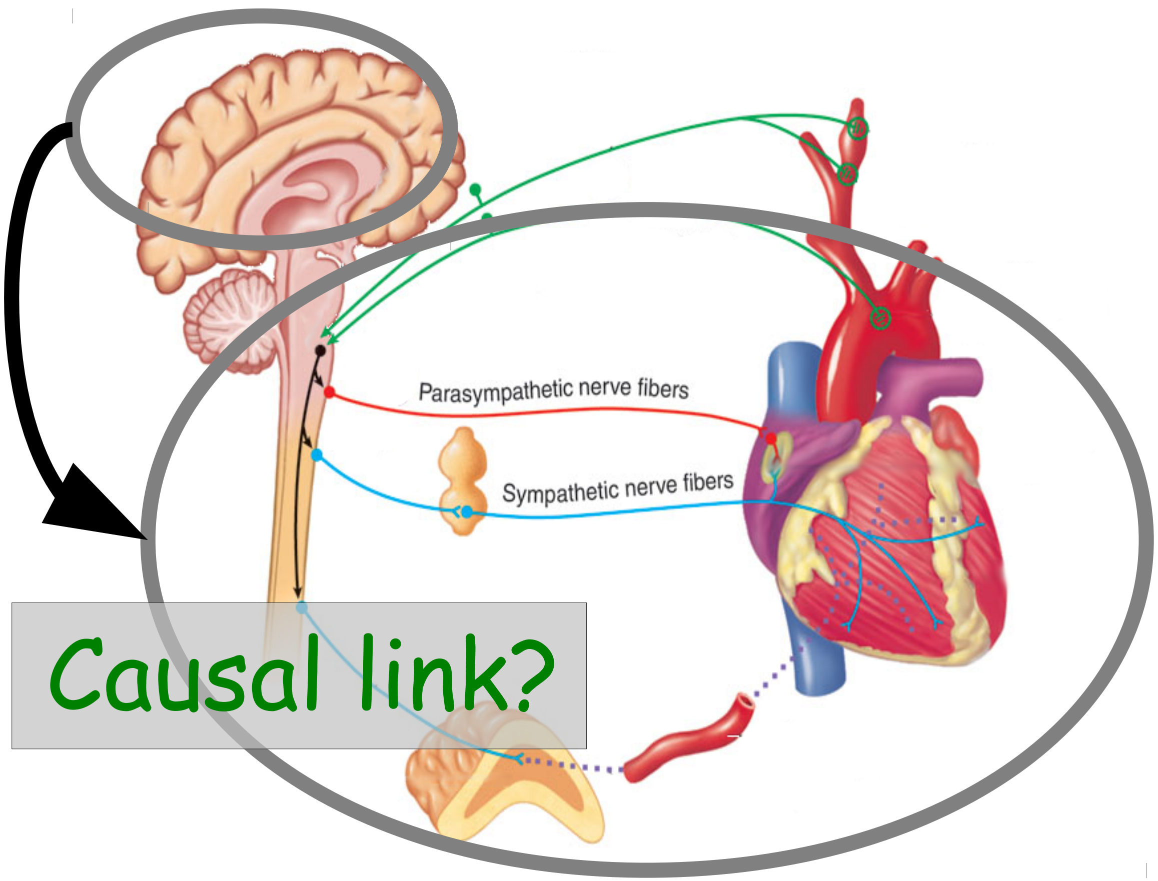

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Challenges in fMRI→ANS causality

7T fMRI

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- Nine healthy volunteers (age 28 ± 3)
- 7 Tesla MRI with simultaneous physiological signal acquisition (1 kHz sampling of cardiac pulsations)
- Single-shot 2D EPI readout
- TR =1.5 s, Voxel 1.8 mm^3, whole brain coverage which minimized aliasing in ANS frequency bands
- Slice timing, motion correction, co-registration to MNI space, physiological noise correction (high-pass filtering at 0.01Hz and removal of 2nd ord. RETROICOR regressors)
- Average BOLD signal extracted in 117 regions of interest (ROIs) with the Automated Anatomical Labeling (AAL) atlas.

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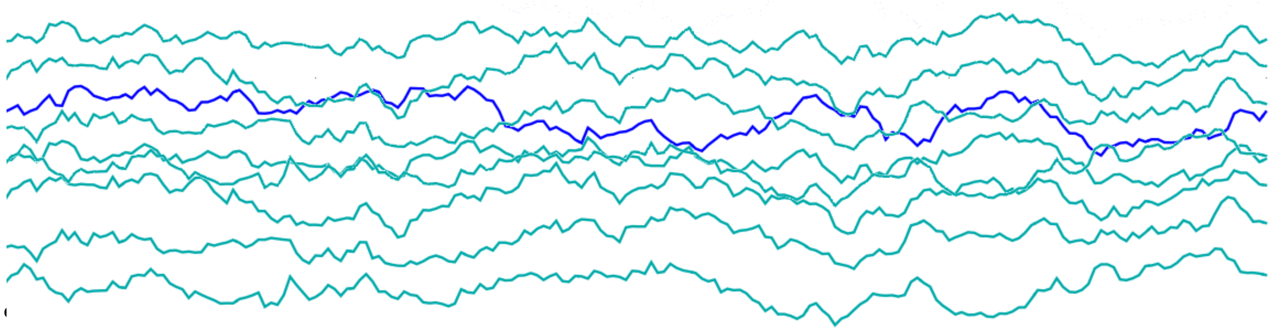

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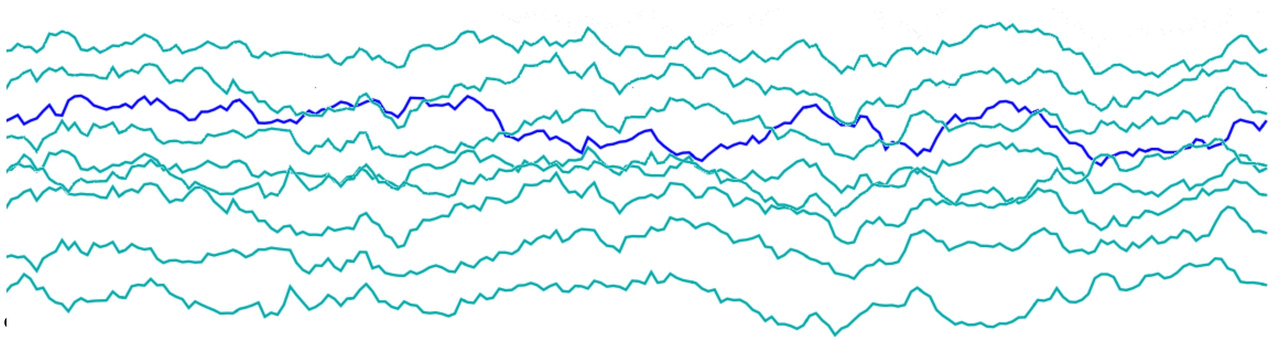
Challenges in fMRI→ANS causality

7T fMRI with physiological signals



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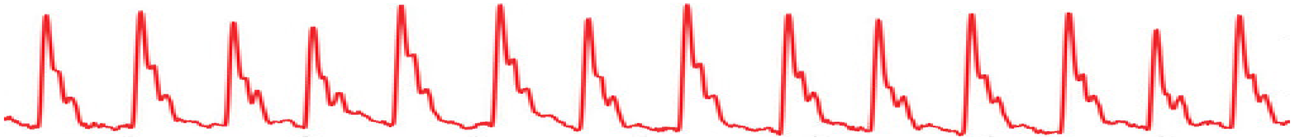

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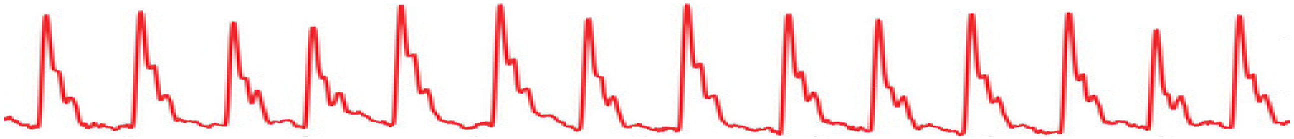

- Probability of next R-wave:

$$f(t \mid \mathrm{H}_t, \xi(t)) = \left[\frac{\xi_0(t)}{2\pi(t-u_{N(t)})^3}\right]^{\frac{1}{2}} \times$$

$$\times \exp\left\{-\frac{1}{2}\frac{\xi_0(t)[t-u_{N(t)}-\mu_{RR}(t,\mathrm{H}_t,\xi(t))]^2}{\mu_{RR}(t,\mathrm{H}_t,\xi(t))^2(t-u_{N(t)})}\right\}$$

- Model RR interval:

$$\mu_{\mathrm{RR}}(t,\mathrm{H}_t,\xi(t)) = \mathrm{RR}_{N(t)-1} + \gamma_0(t) + \sum_{i=1}^{p}\gamma_1(i,t)\,\Delta\mathrm{RR}_i + \grave{\alpha}(t)$$

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Challenges in fMRI→ANS causality

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- Analytical power spectrum from parameters

- SNR in fMRI, time-resolution
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- Analytical power spectrum from parameters

- Time varying estimation of:
  - HF (parasimpathetic)
  - LF (sympathetic + parasympathetic)
  - Sympathovagal balance (LF/HF)

- SNR in fMRI, time-resolution

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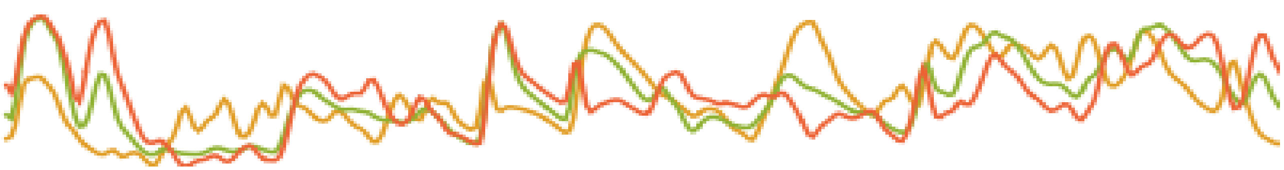
Challenges in fMRI→ANS causality



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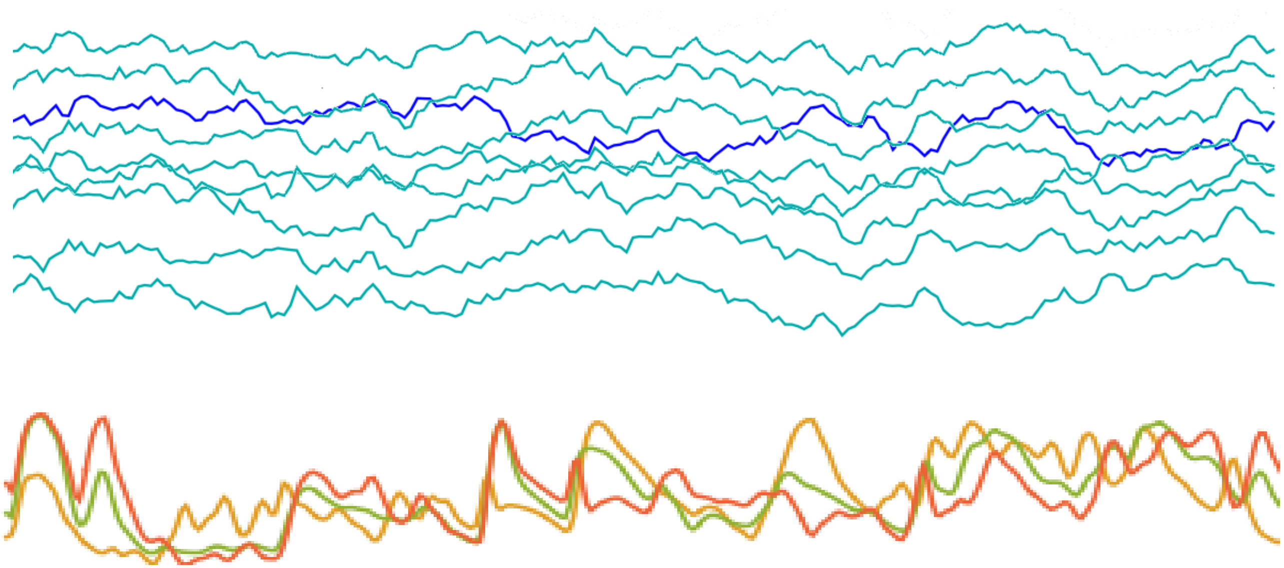

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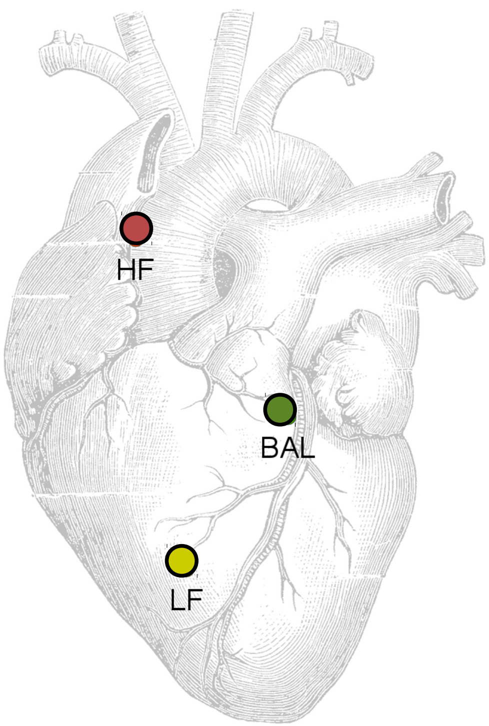

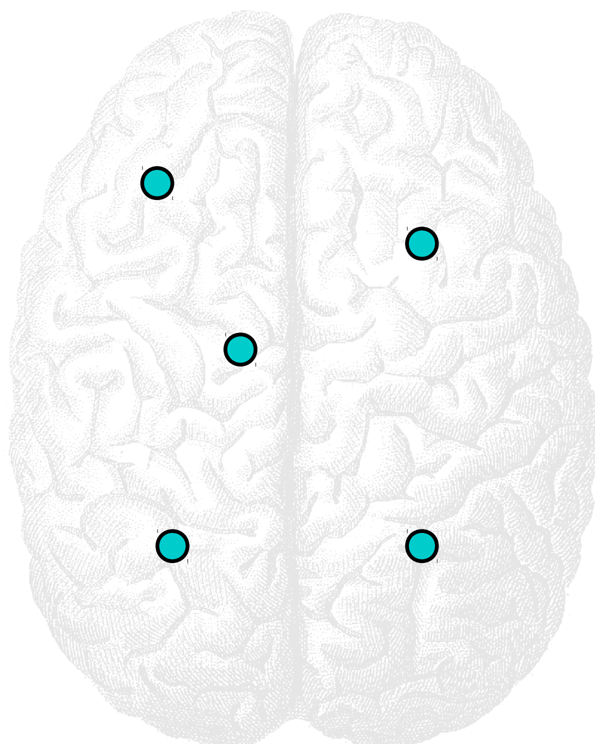

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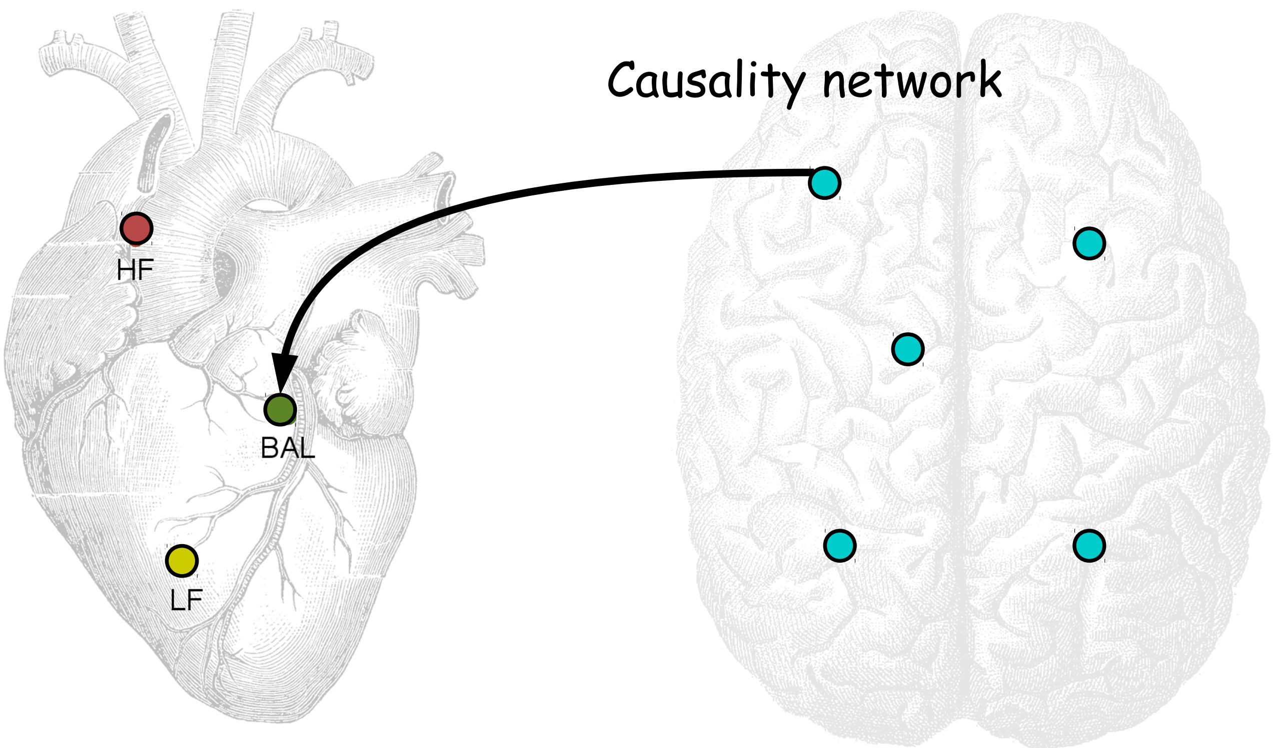

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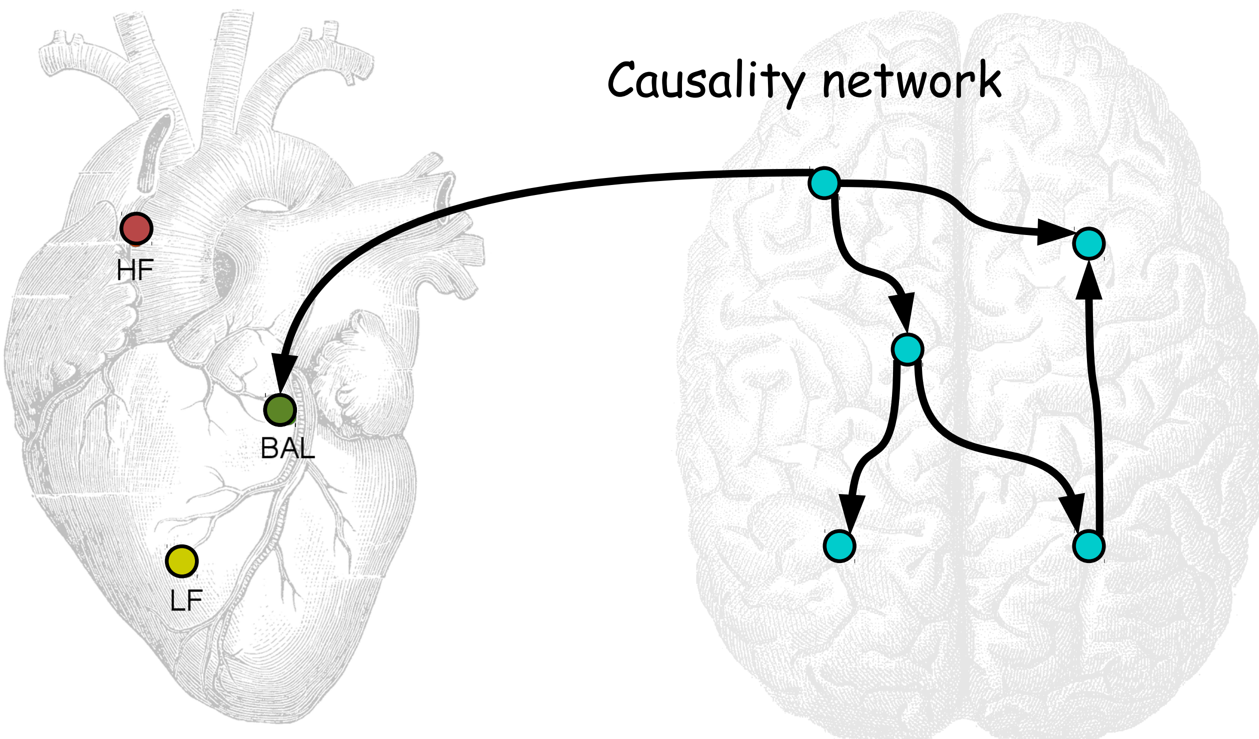

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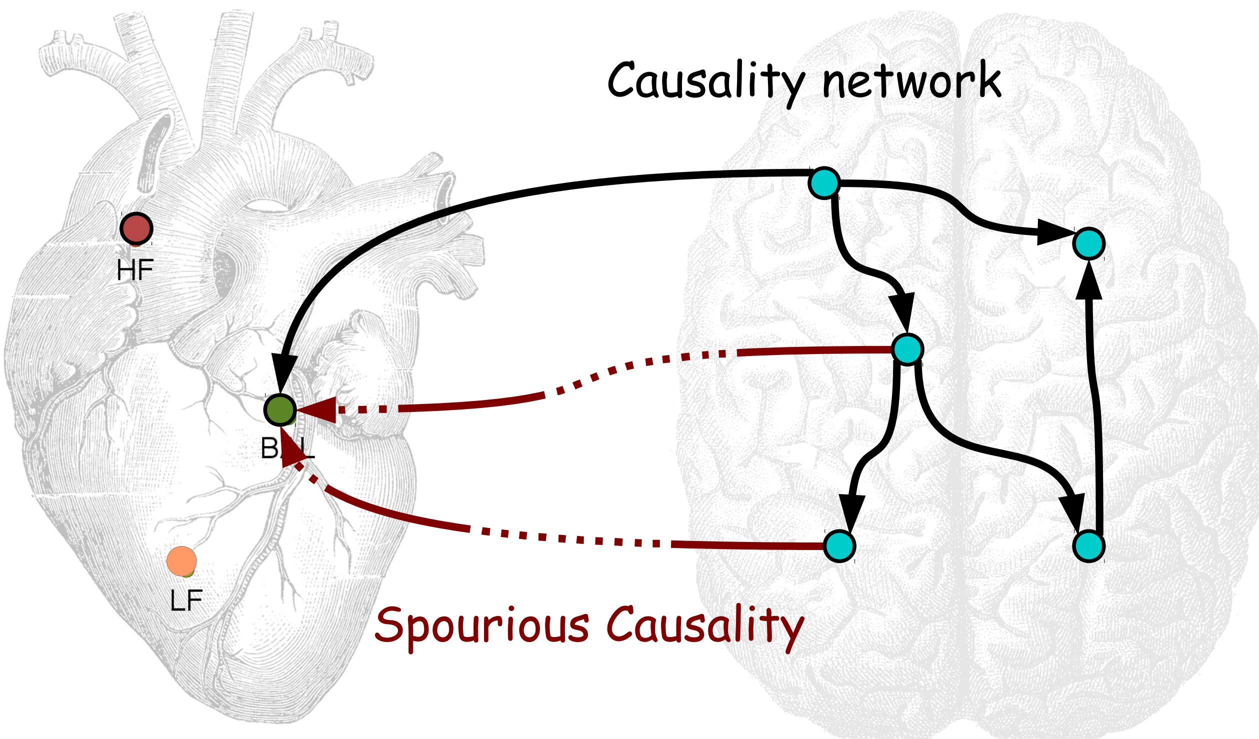

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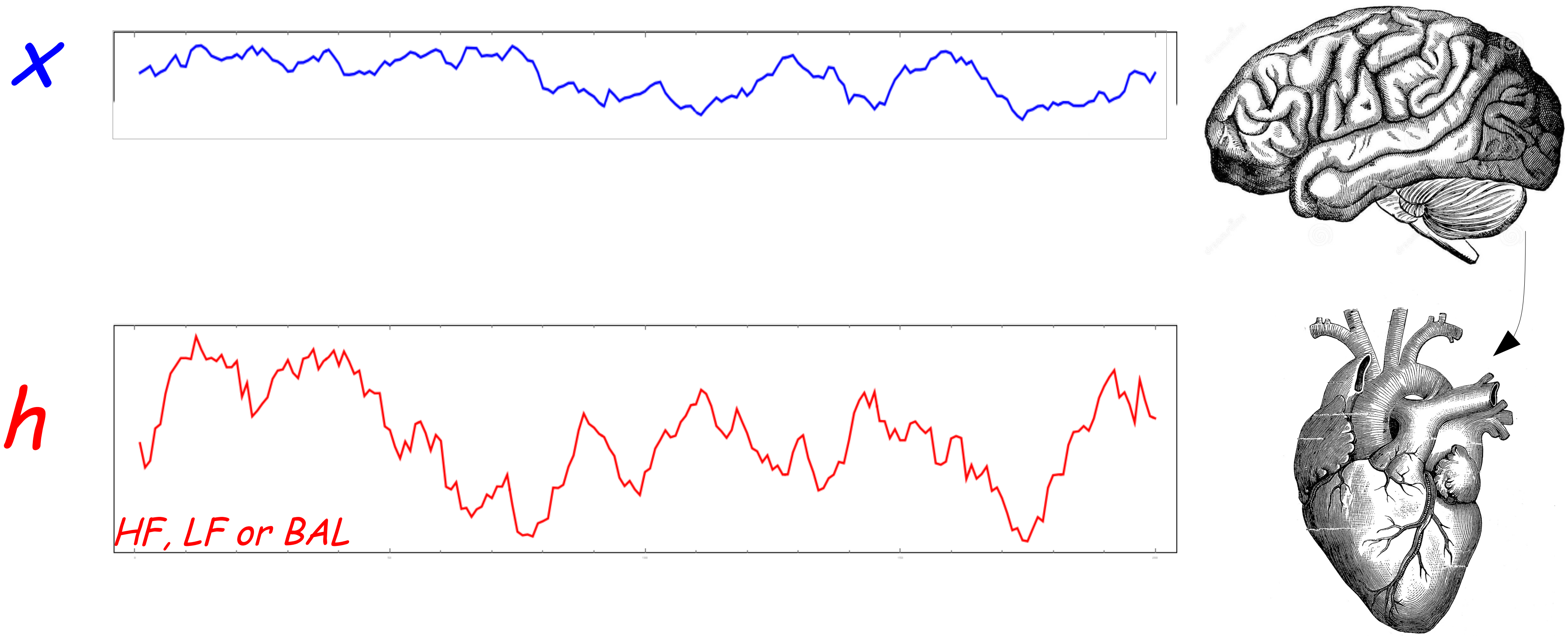
Granger causality (at a glance)



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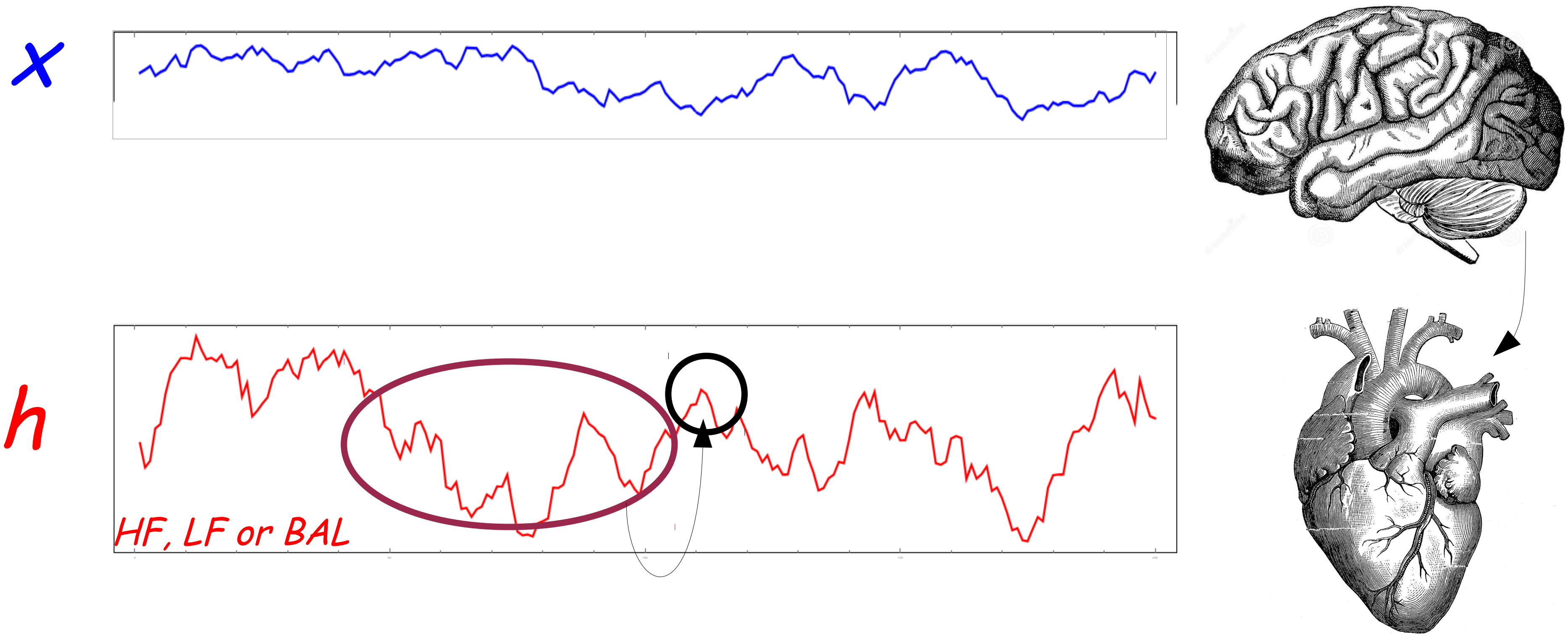

$$h_{now} = F(h_{before}) + \text{(noise)}$$

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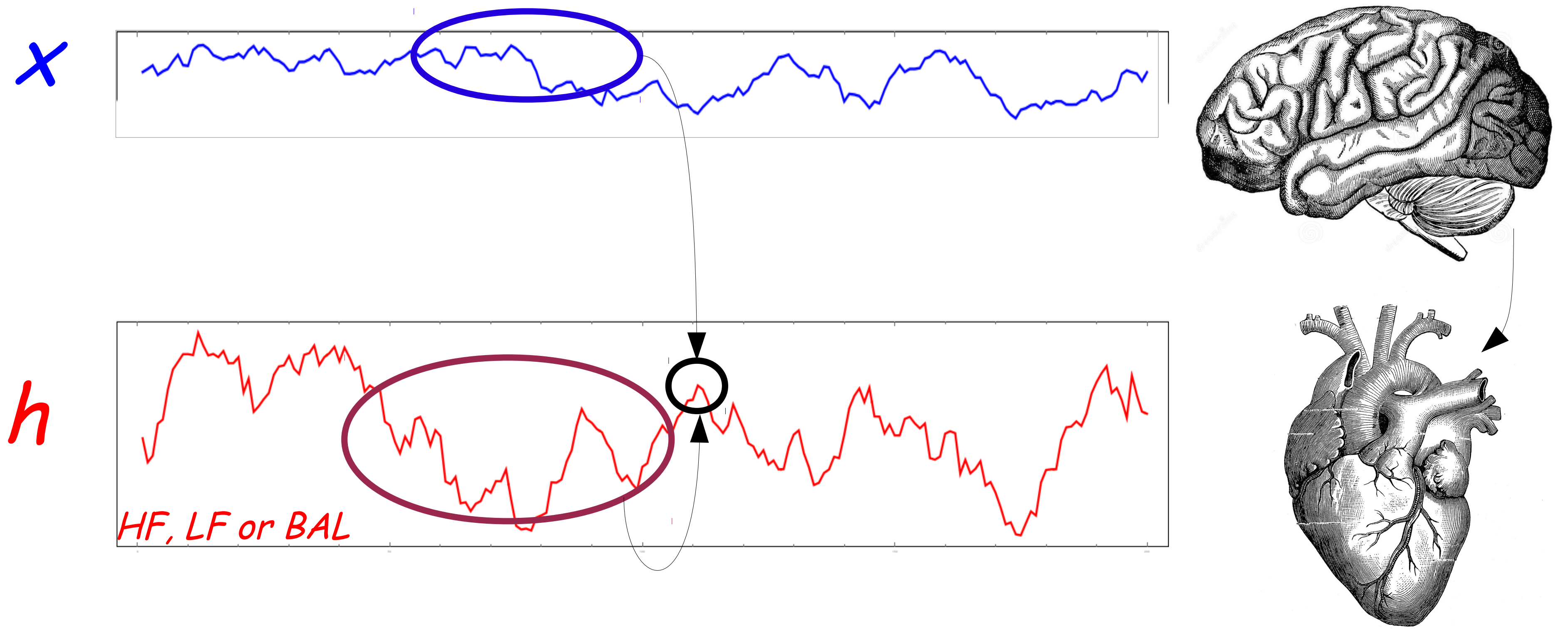

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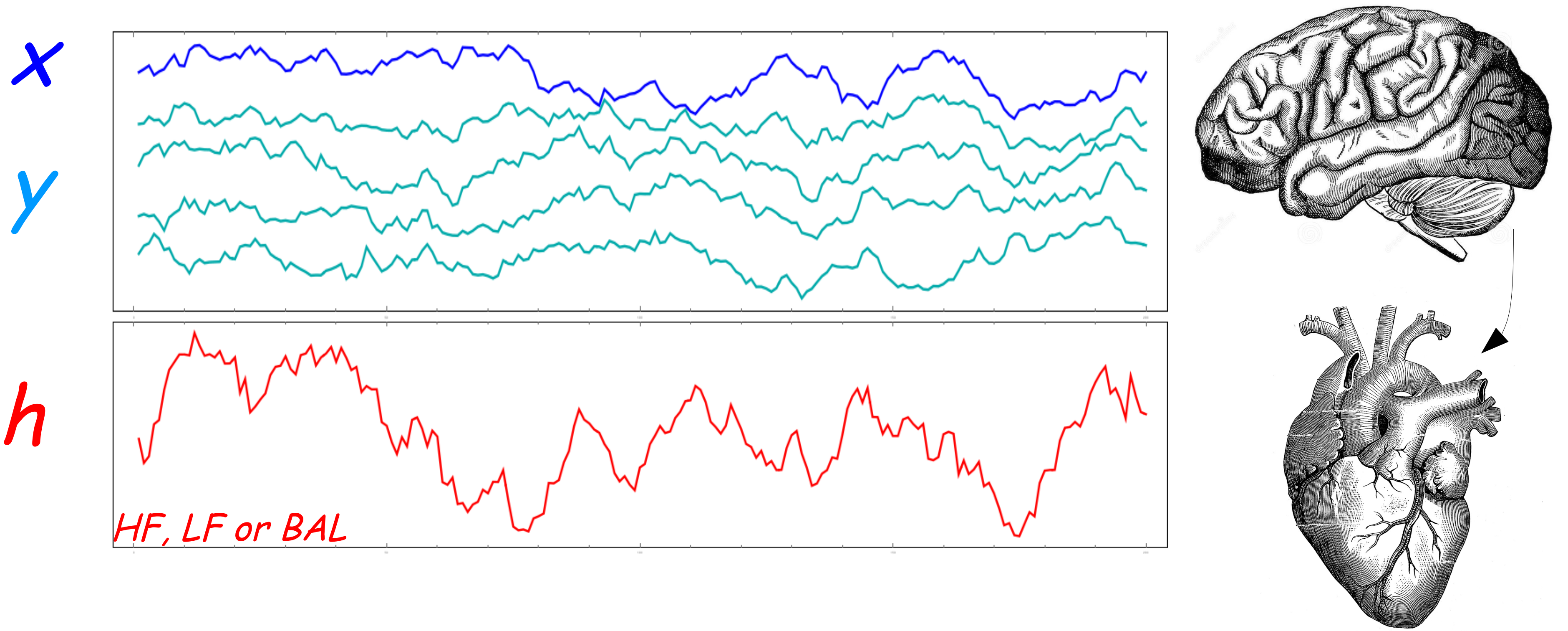

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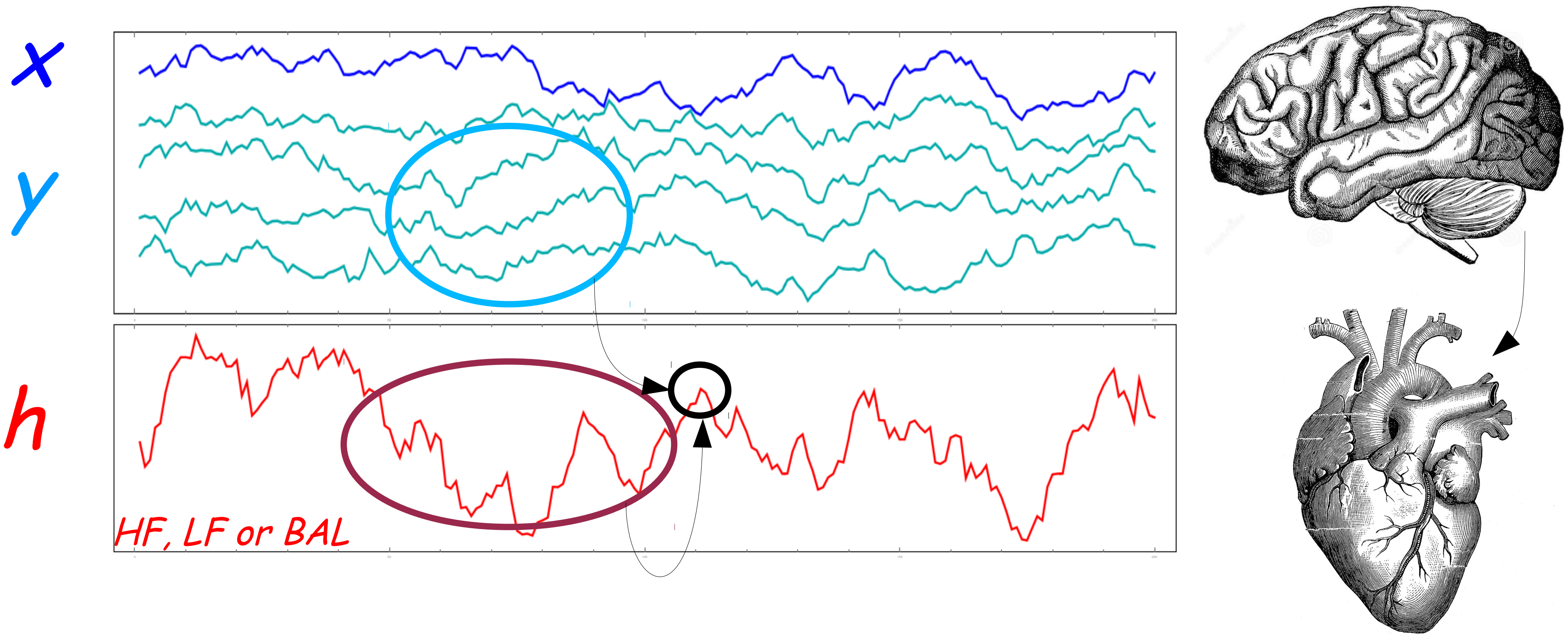

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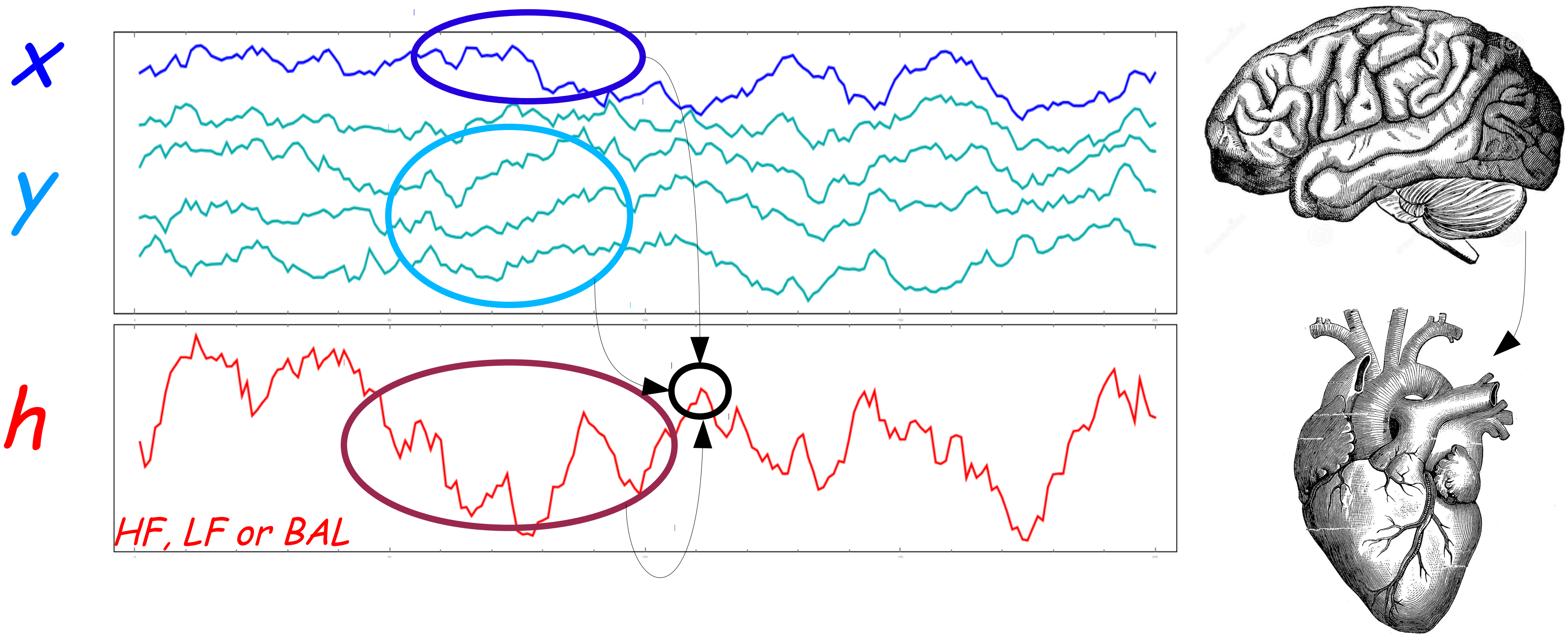

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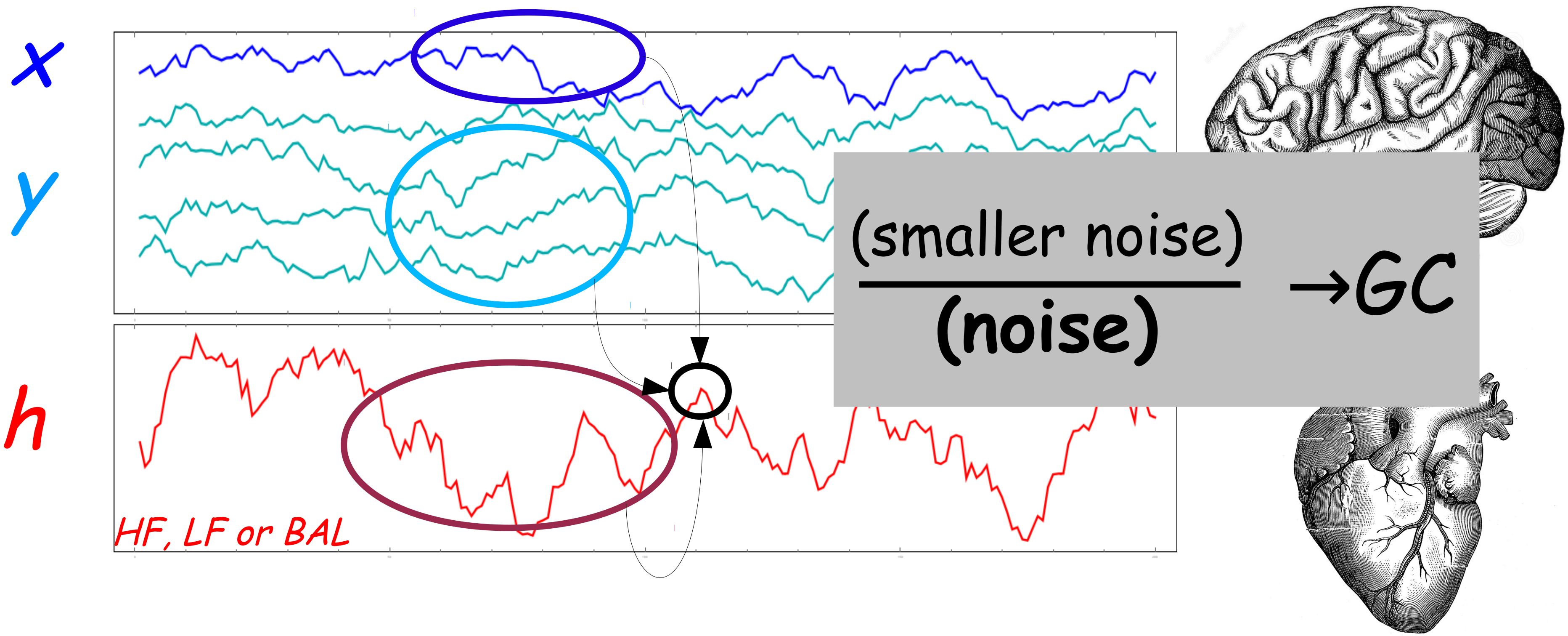

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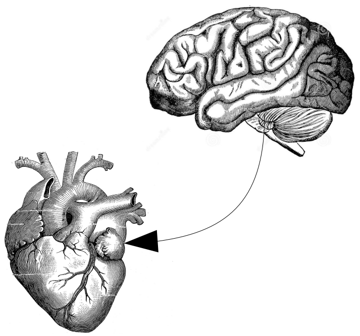
Globally Conditioned Granger Causality

$$H_{\mathrm{HF}}(t) = \sum_{q=1}^{Q} b'_q H_{\mathrm{HF}}(t-q) + \sum_{p=1}^{P} \sum_{\substack{k=1 \\ k \neq j}}^{117} a'_{k,p} x_k(t-p) + \varepsilon'_t$$



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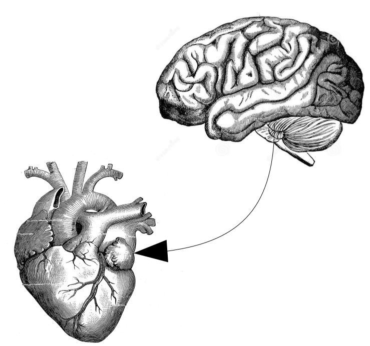

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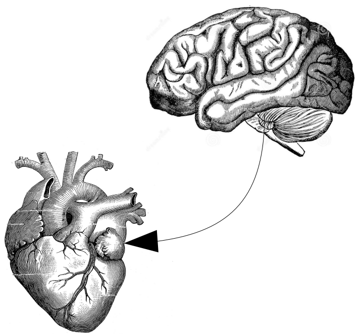

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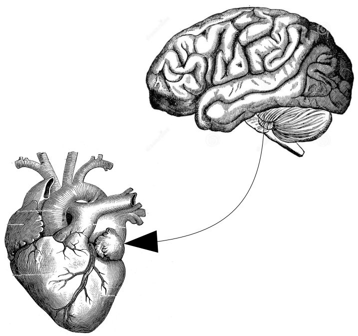

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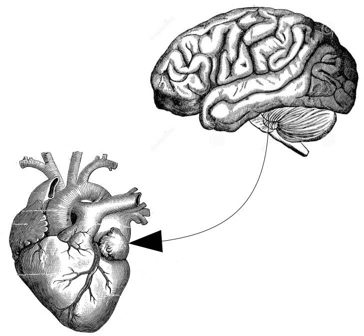

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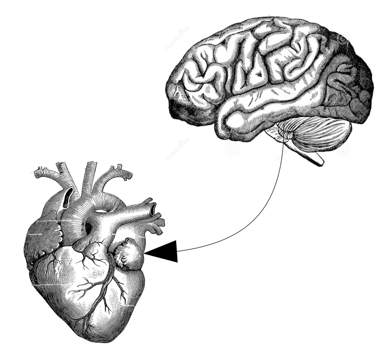
Globally Conditioned Granger Causality

$h_{now} = F(h_{before}) + I(y_{before}) + \text{(noise)}$

$h_{now} = F(h_{before}) + I(y_{before}) + G(x_{before}) + \text{(smaller noise)}$

117 anatomically labelled region of interest

$$H_{\mathrm{HF}}(t) = \sum_{q=1}^{Q} b'_q H_{\mathrm{HF}}(t-q) + \sum_{p=1}^{P} \sum_{\substack{k=1 \\ k \neq j}}^{117} a'_{k,p} x_k(t-p) + \varepsilon'_t$$



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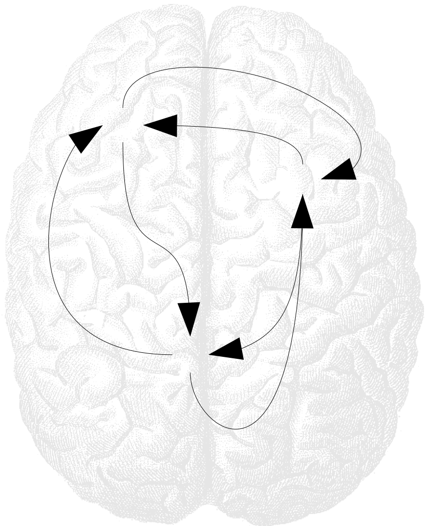
Globally Conditioned Granger Causality



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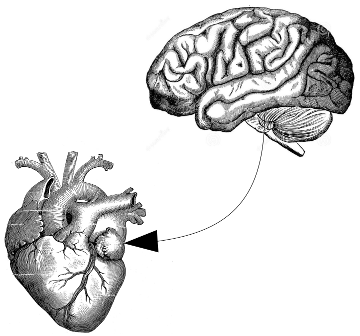

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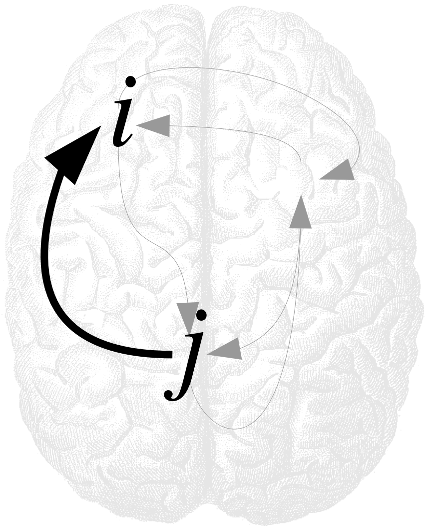
Globally Conditioned Granger Causality



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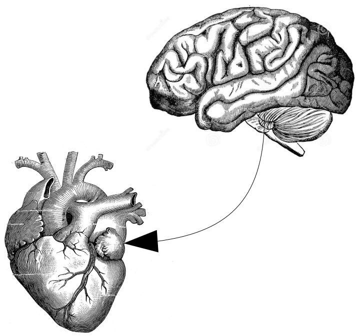

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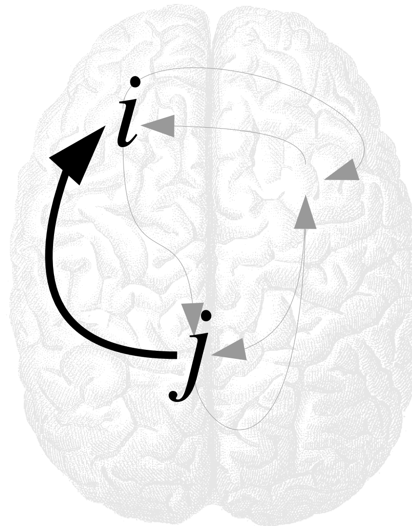

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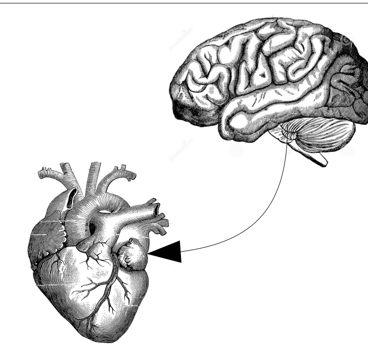

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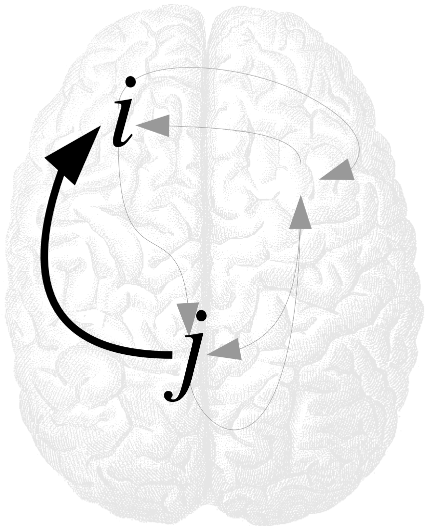

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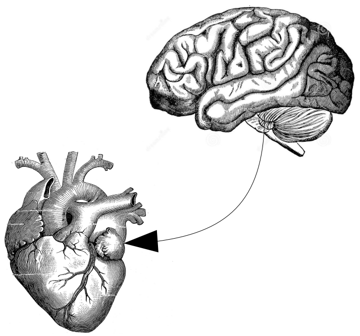

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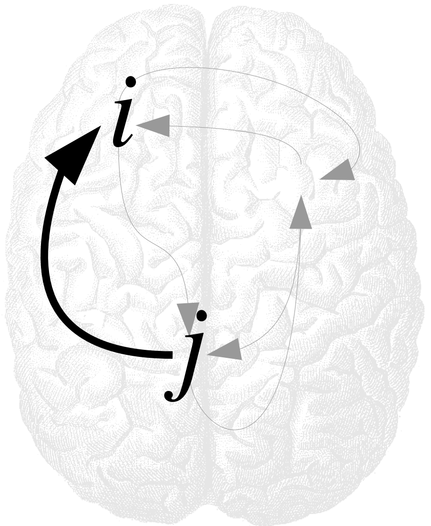

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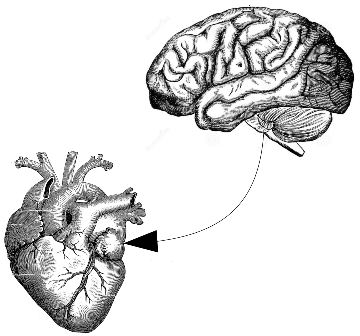

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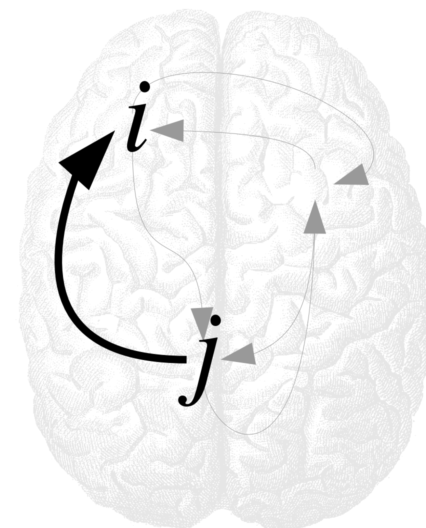

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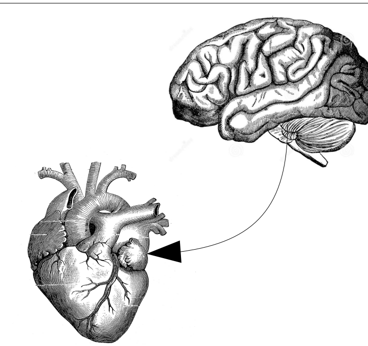

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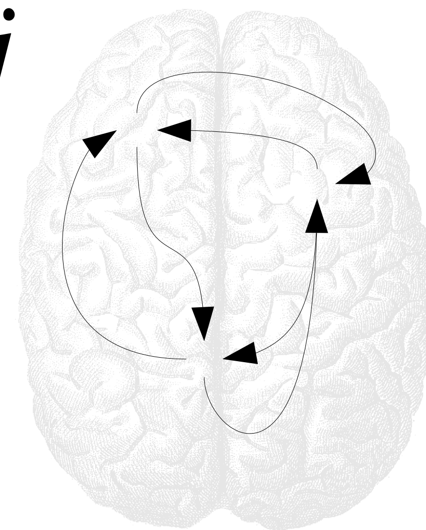
Globally Conditioned Granger Causality

$\forall\ i,j$



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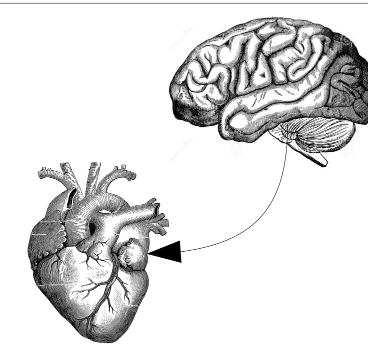

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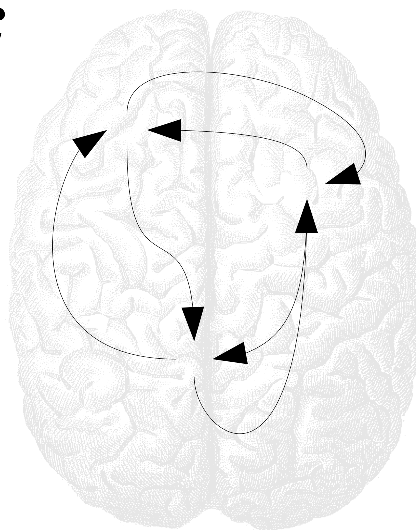
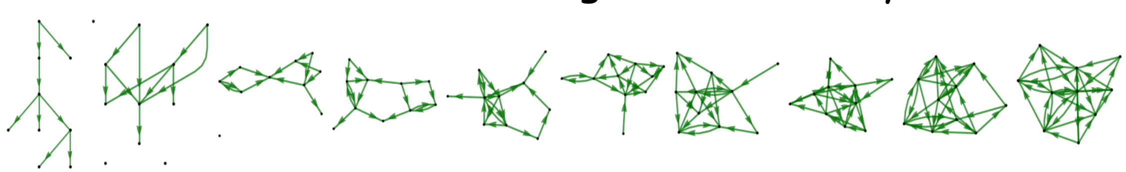


Different network tested for generation of synthetic data



Globally Conditioned Granger Causality

$\forall\ i,j$

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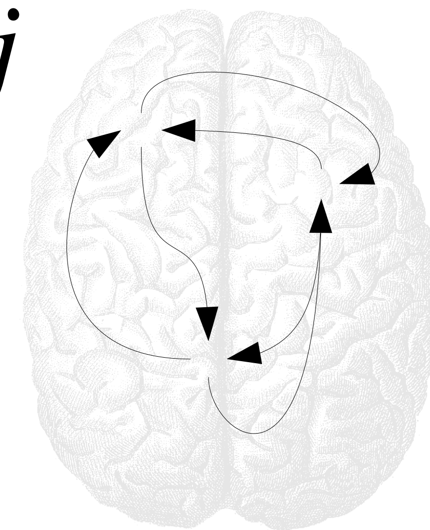

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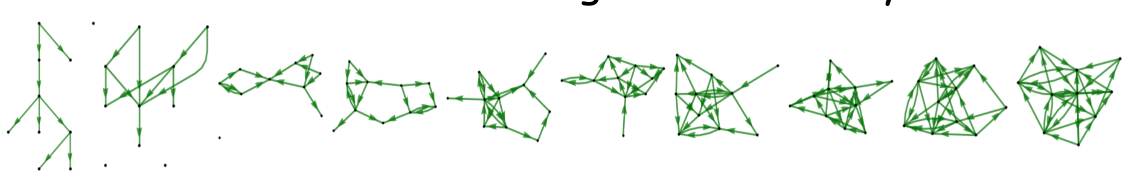

Duffing oscillator

$$\dot{x}_i = y + k_{i,j}(x_j - x_i)$$

$$\dot{y}_i = \delta y_i - \beta x_i - \alpha x^3 - \gamma \cos(\omega_i t + \phi_i)$$

Globally Conditioned Granger Causality

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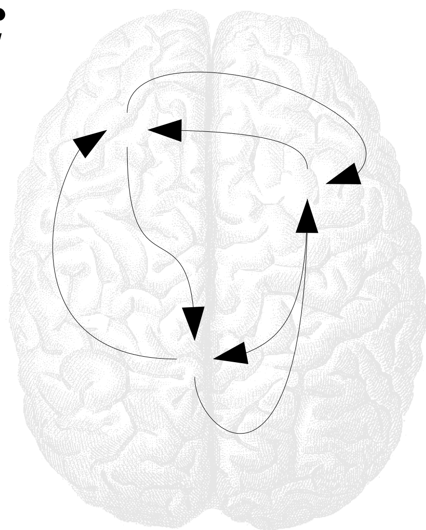

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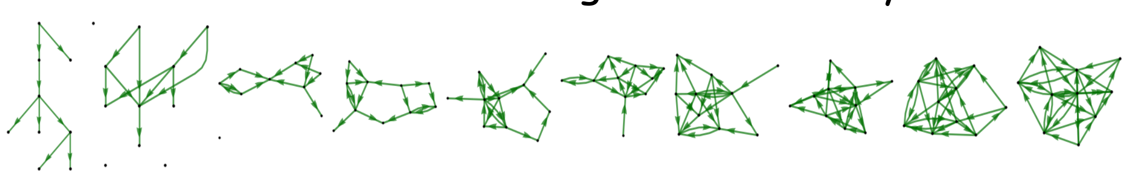

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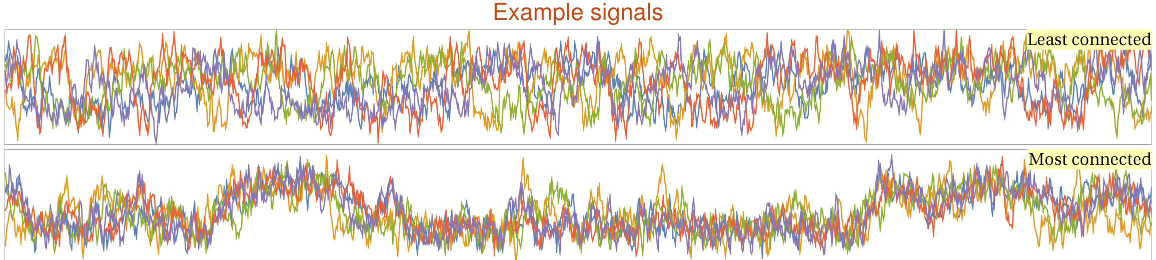
Example signals



Globally Conditioned Granger Causality

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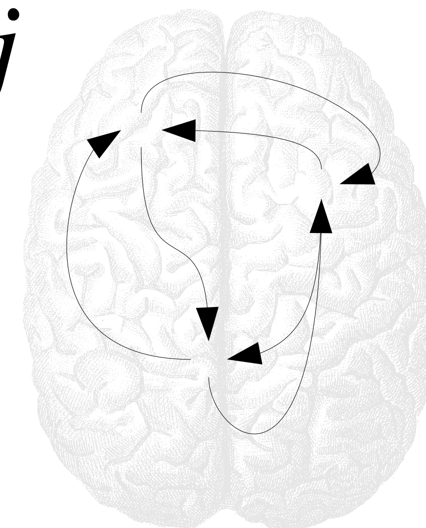
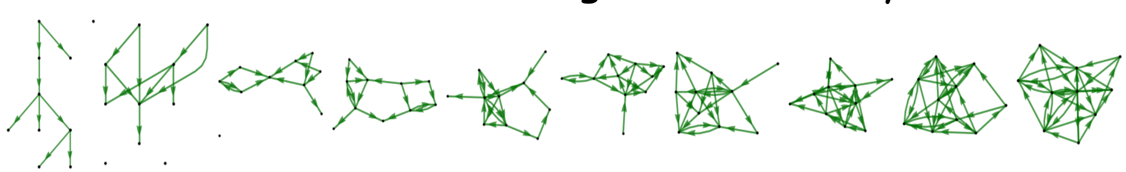


Different network tested for generation of synthetic data



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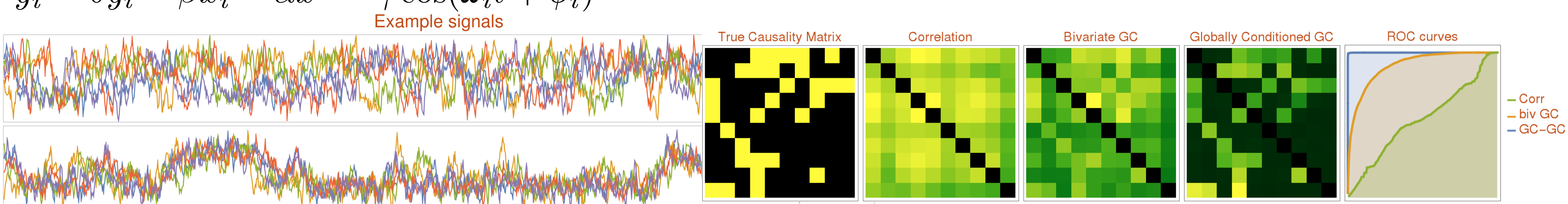

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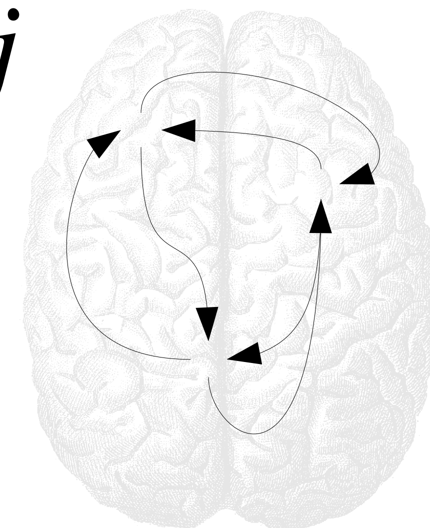

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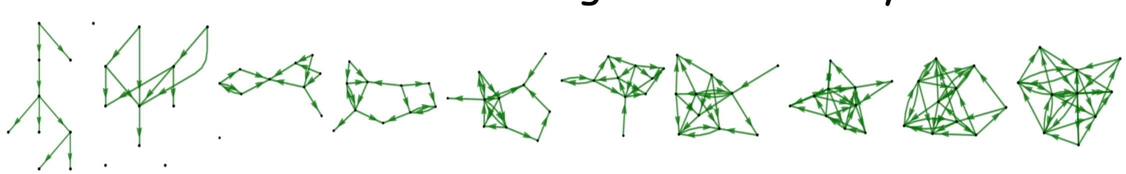
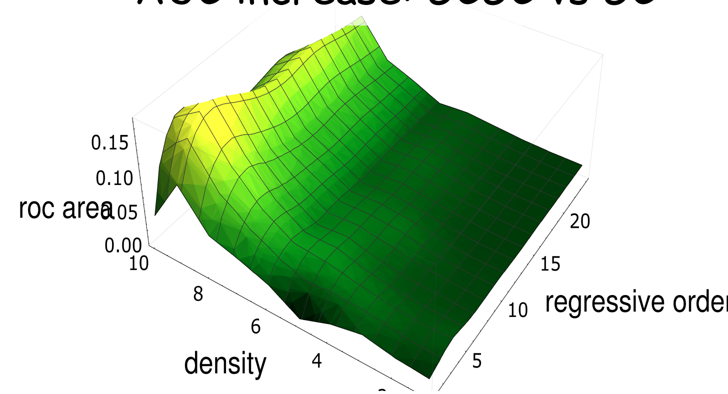


AUC increase: GCGC vs GC



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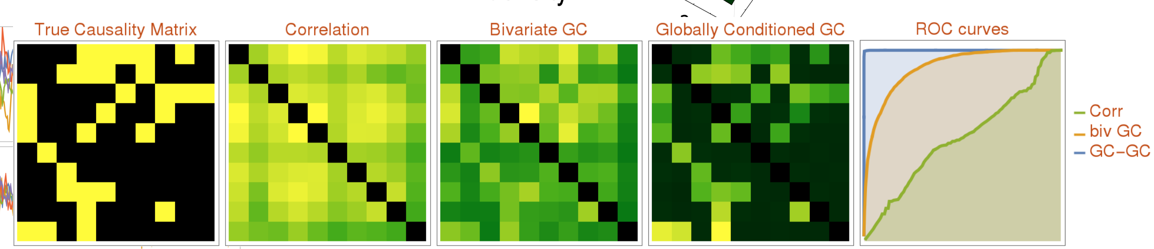
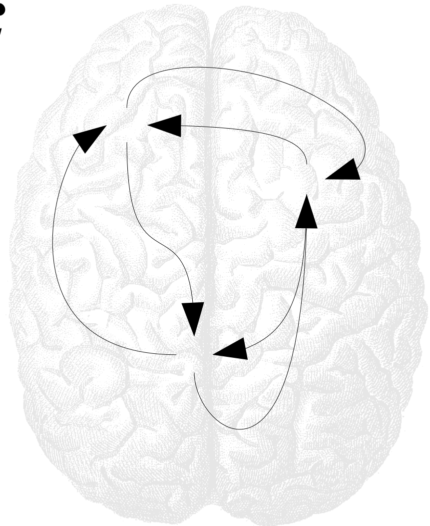


Globally Conditioned Granger Causality

$\forall\ i,j$



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Statistics of the residuals

$$\frac{(\varepsilon' - \varepsilon)}{\varepsilon} \frac{\mathrm{DOF}' - \mathrm{DOF}}{\mathrm{DOF}} \sim \frac{\chi^2_{DOF'-DOF}}{\chi^2_{DOF}} \sim \text{F-distrib}$$

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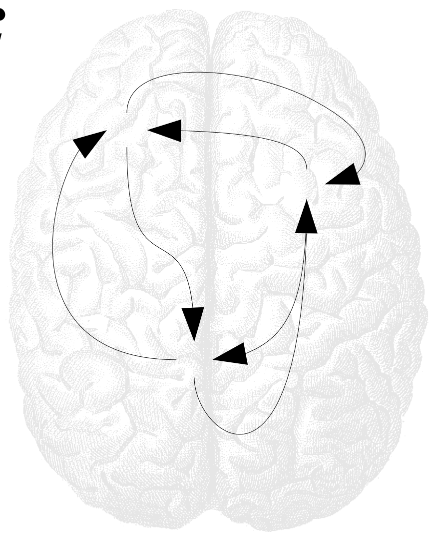

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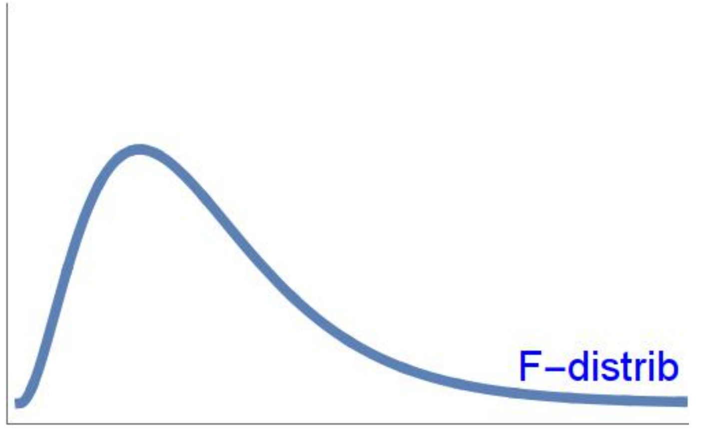

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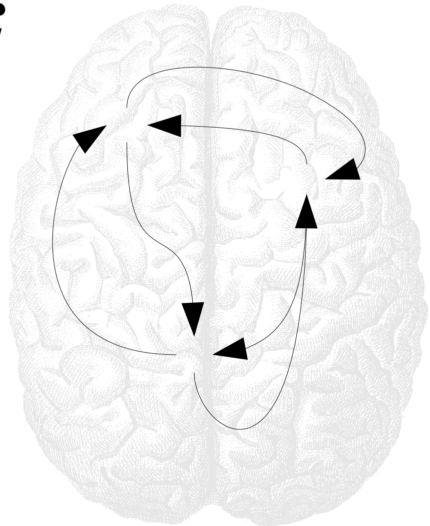
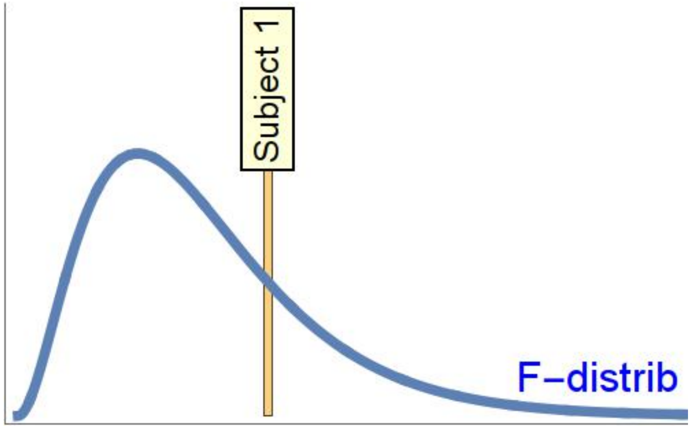


The group-wise statistics

$$\frac{(\varepsilon' - \varepsilon)}{\varepsilon} \frac{\mathrm{DOF}' - \mathrm{DOF}}{\mathrm{DOF}} \sim \frac{\chi^2_{DOF'-DOF}}{\chi^2_{DOF}} \sim \text{F-distrib}$$



Globally Conditioned Granger Causality

$$\forall\ i,j$$

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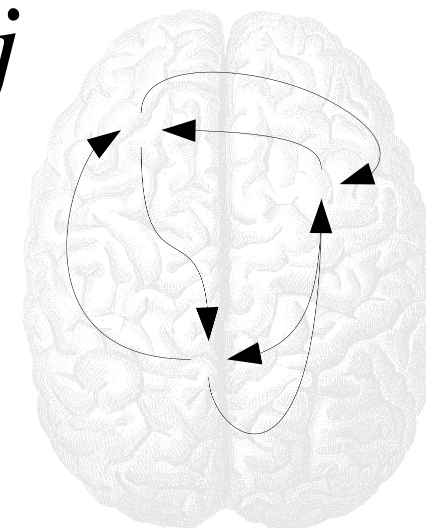
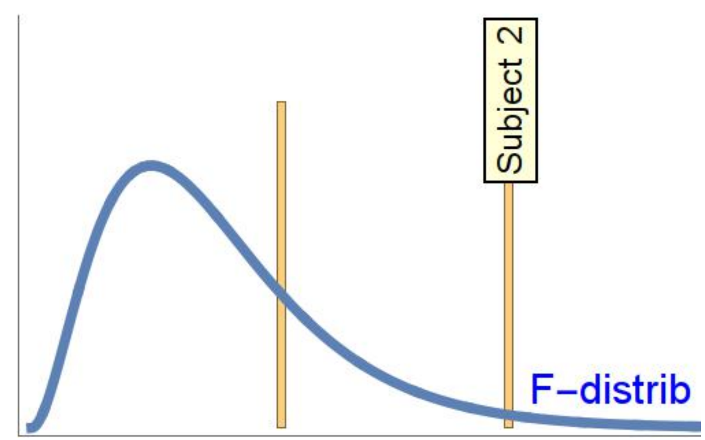


The group-wise statistics

#sub.

$$\frac{(\varepsilon' - \varepsilon)}{\varepsilon} \frac{\mathrm{DOF}' - \mathrm{DOF}}{\mathrm{DOF}} \sim \frac{\chi^2_{DOF'-DOF}}{\chi^2_{DOF}} \sim \text{F-distrib}$$



Globally Conditioned Granger Causality

$$x_i(t) = \sum_{p=1}^{P} \sum_{\substack{k=1 \\ k \neq j}}^{117} a'_{k,p}\, x_k(t-p) + \varepsilon'_t$$

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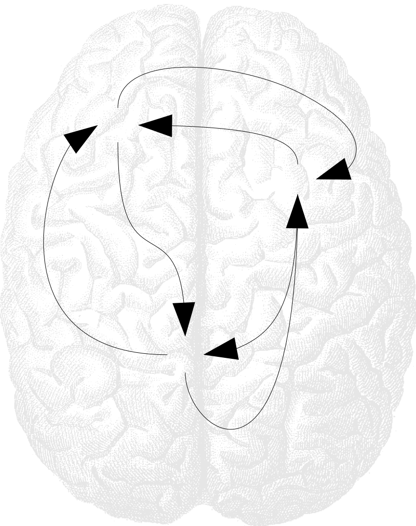
$\forall\ i,j$



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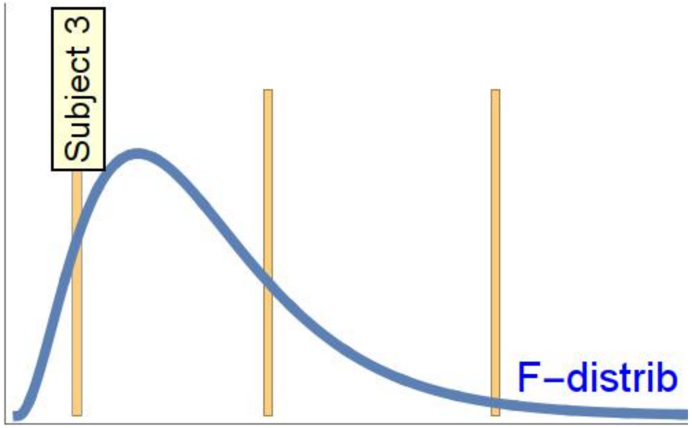

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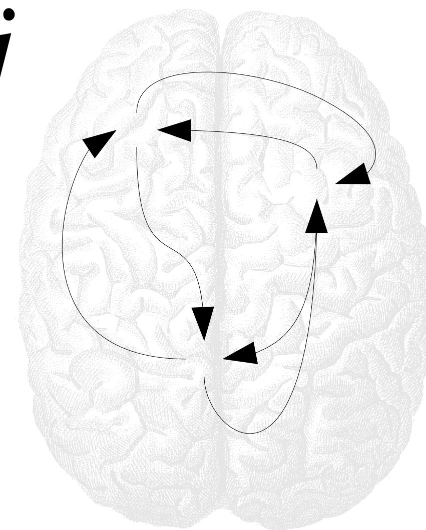

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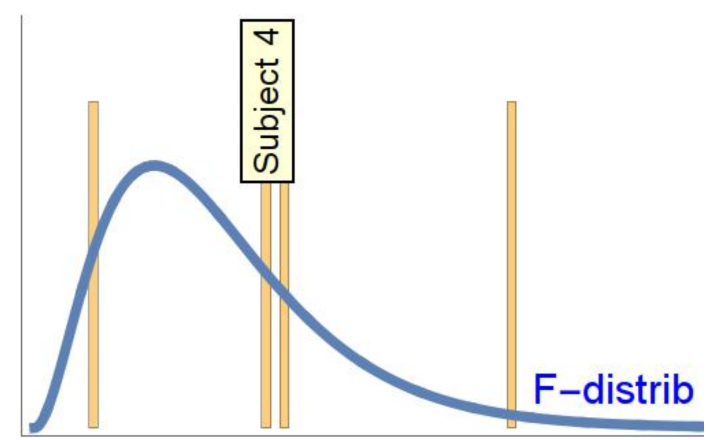

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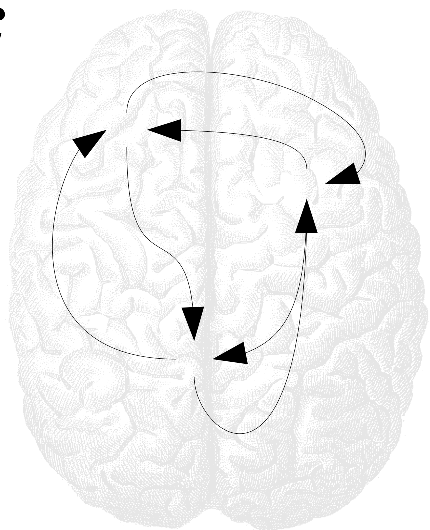

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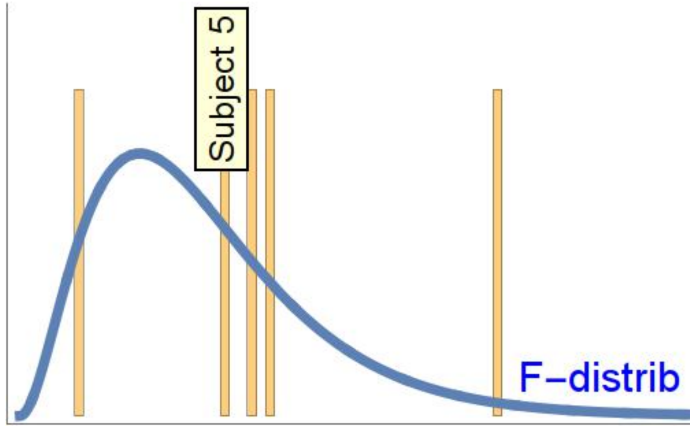

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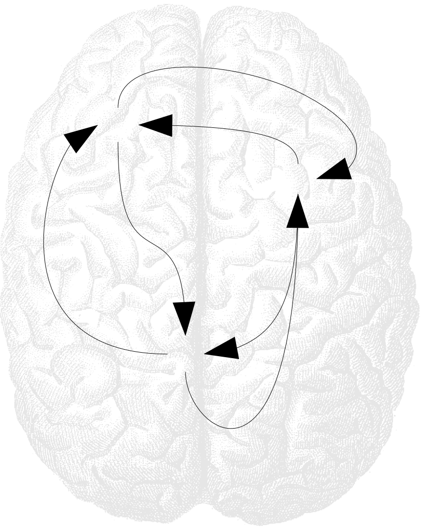

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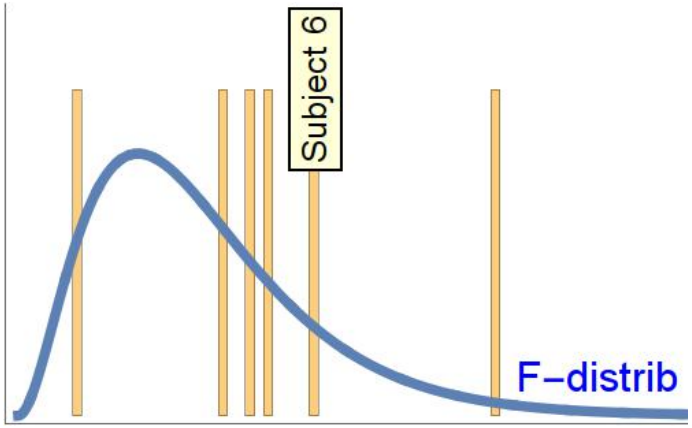

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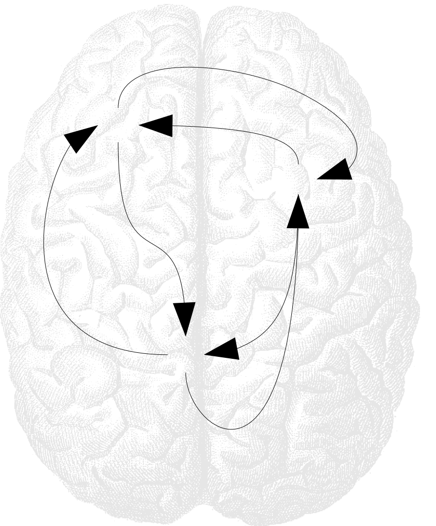

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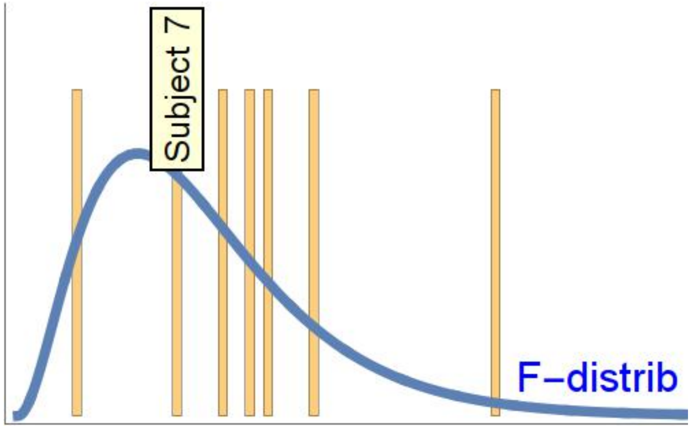

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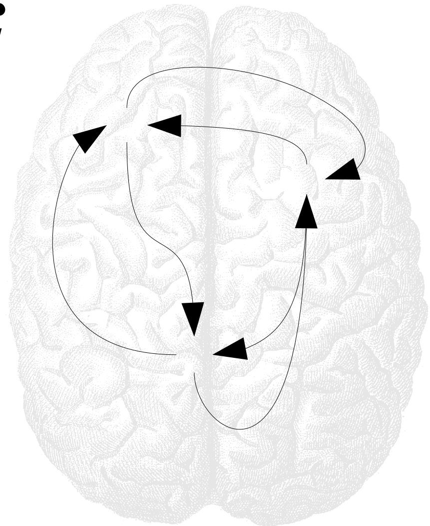

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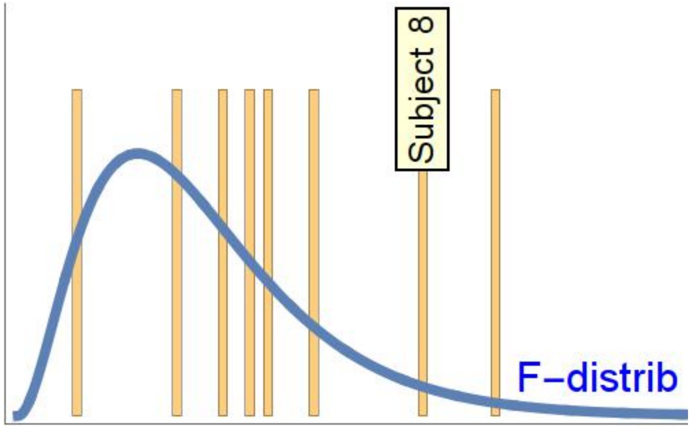

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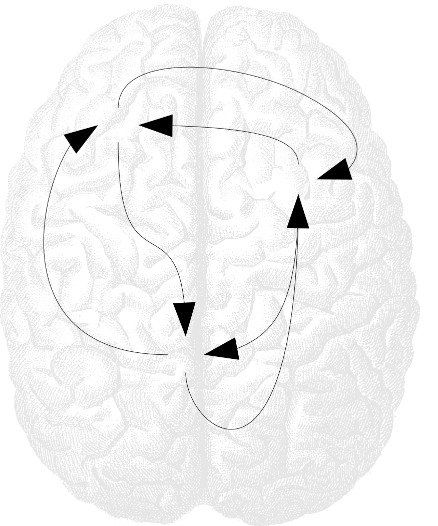

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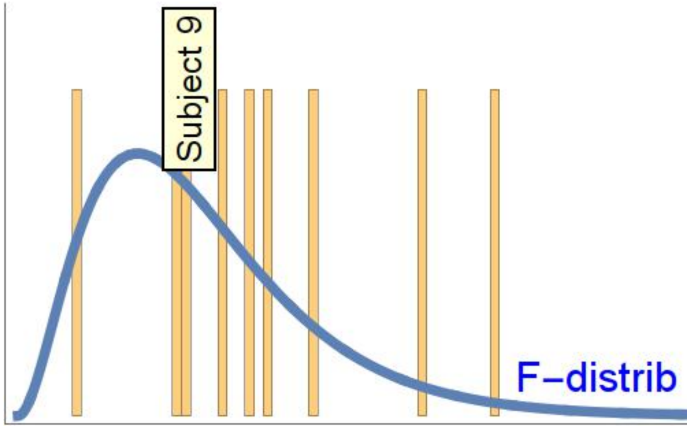

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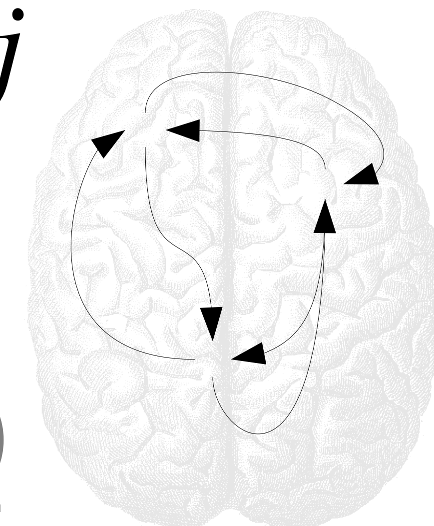

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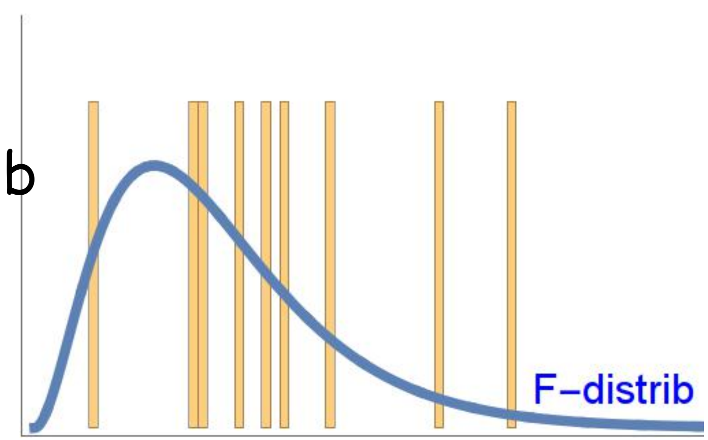
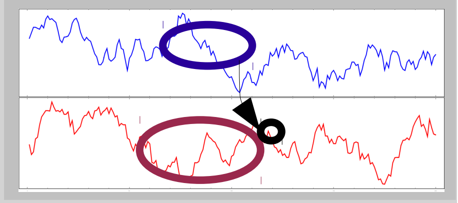
Group-wise median tested again median of F-distrib

(no assumptions about the simmetry of sample distribution)



Results - bivariate GC (Brain → ANS)



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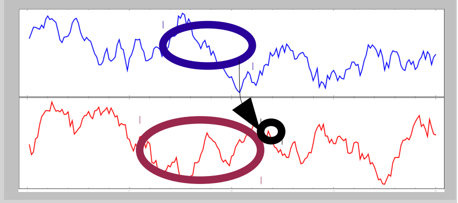
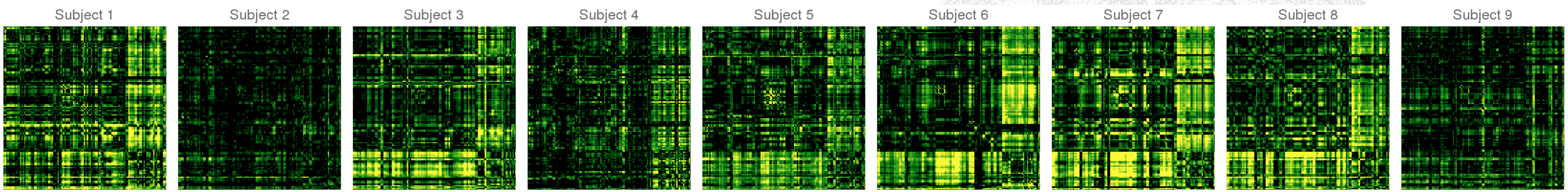
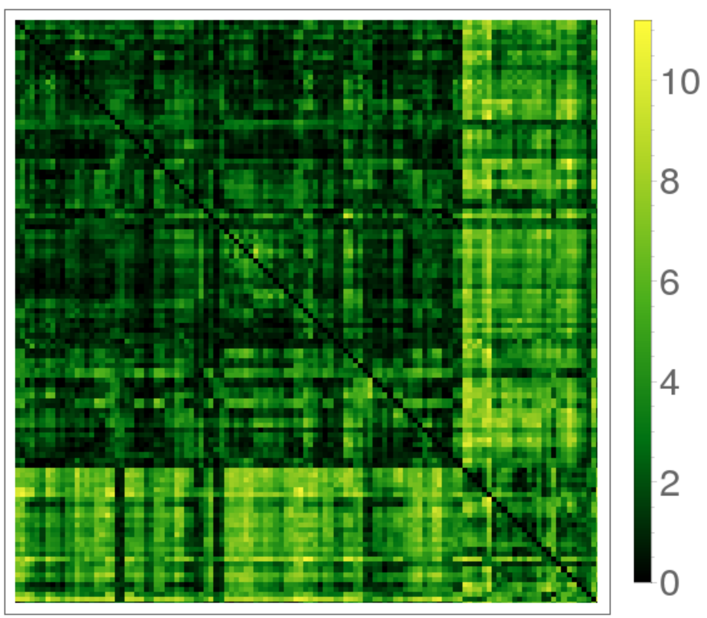


Bivariate GC strenght (brain-brain)



Average GC strenght (brain-brain)



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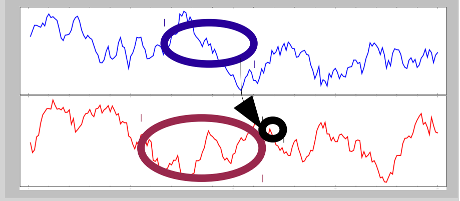

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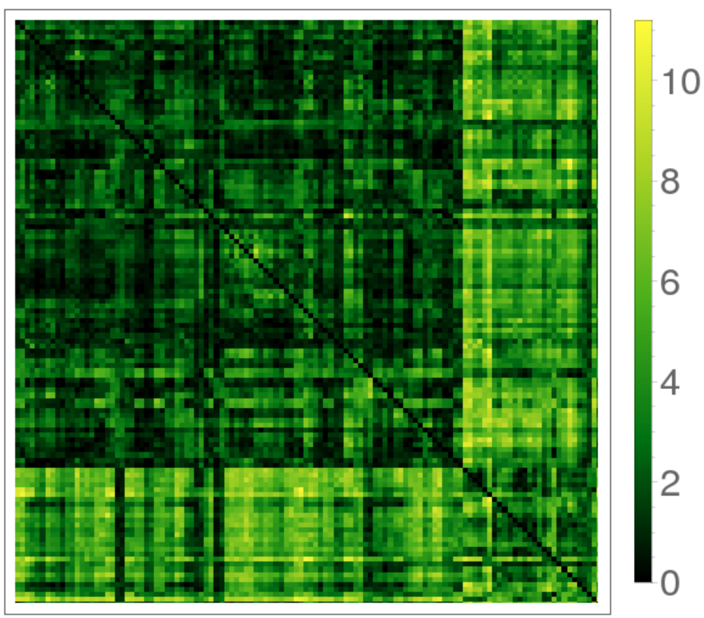
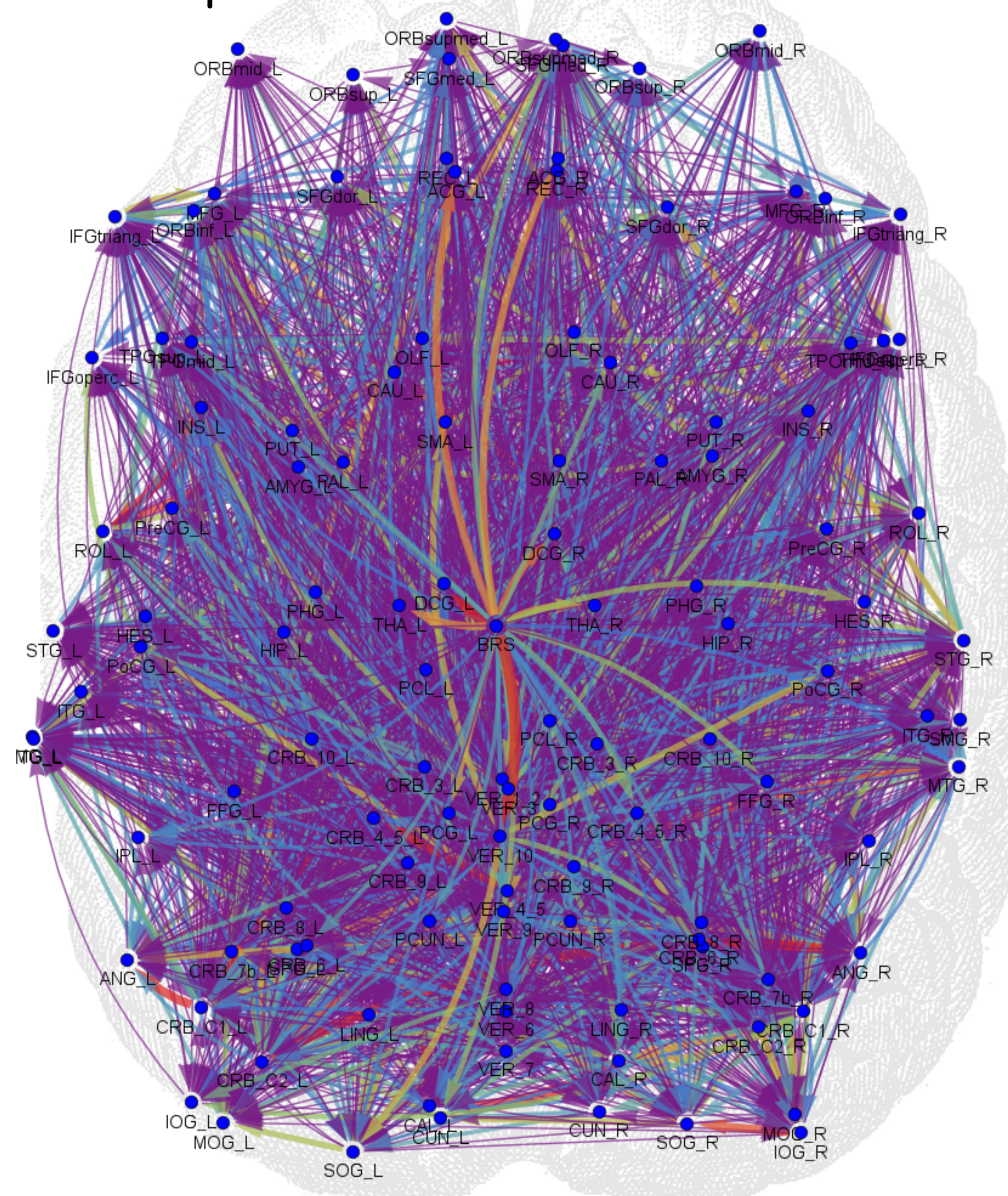


p-value based GC network



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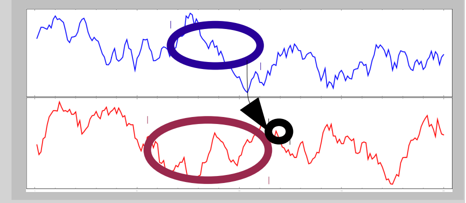

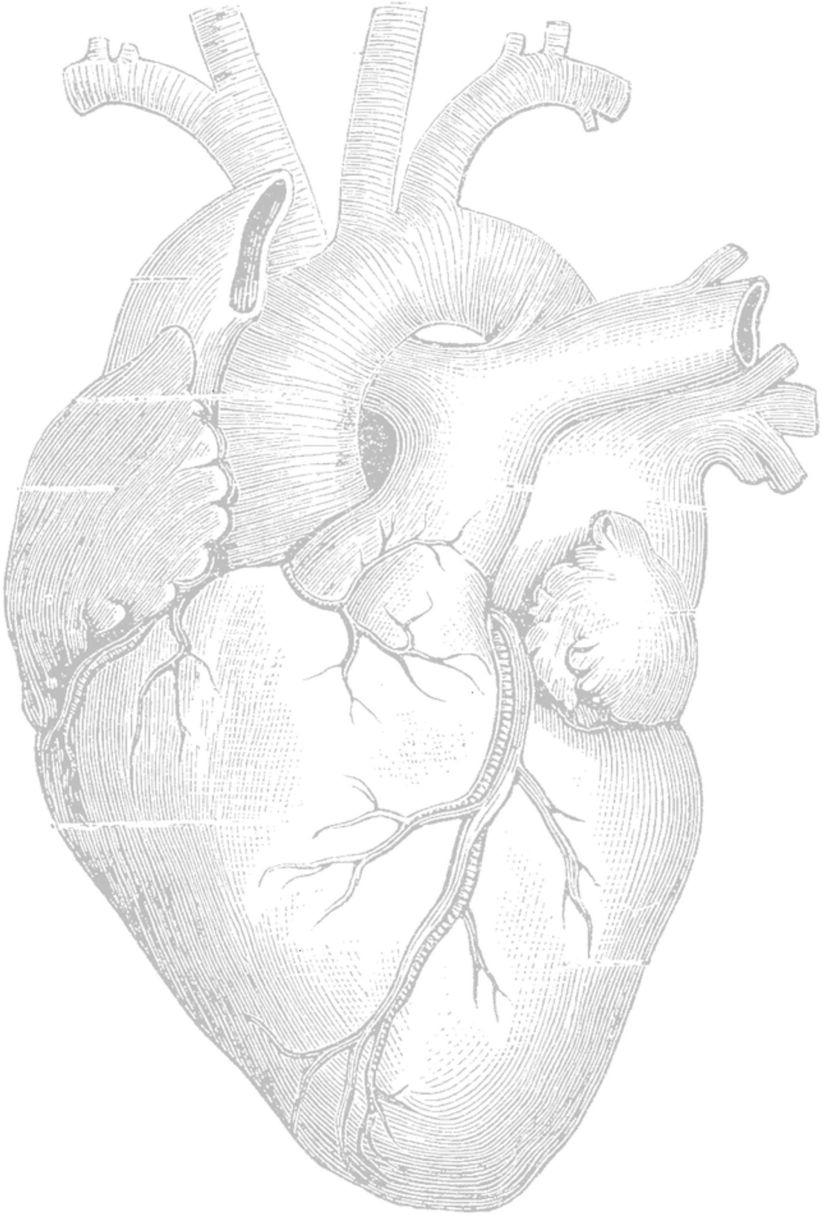

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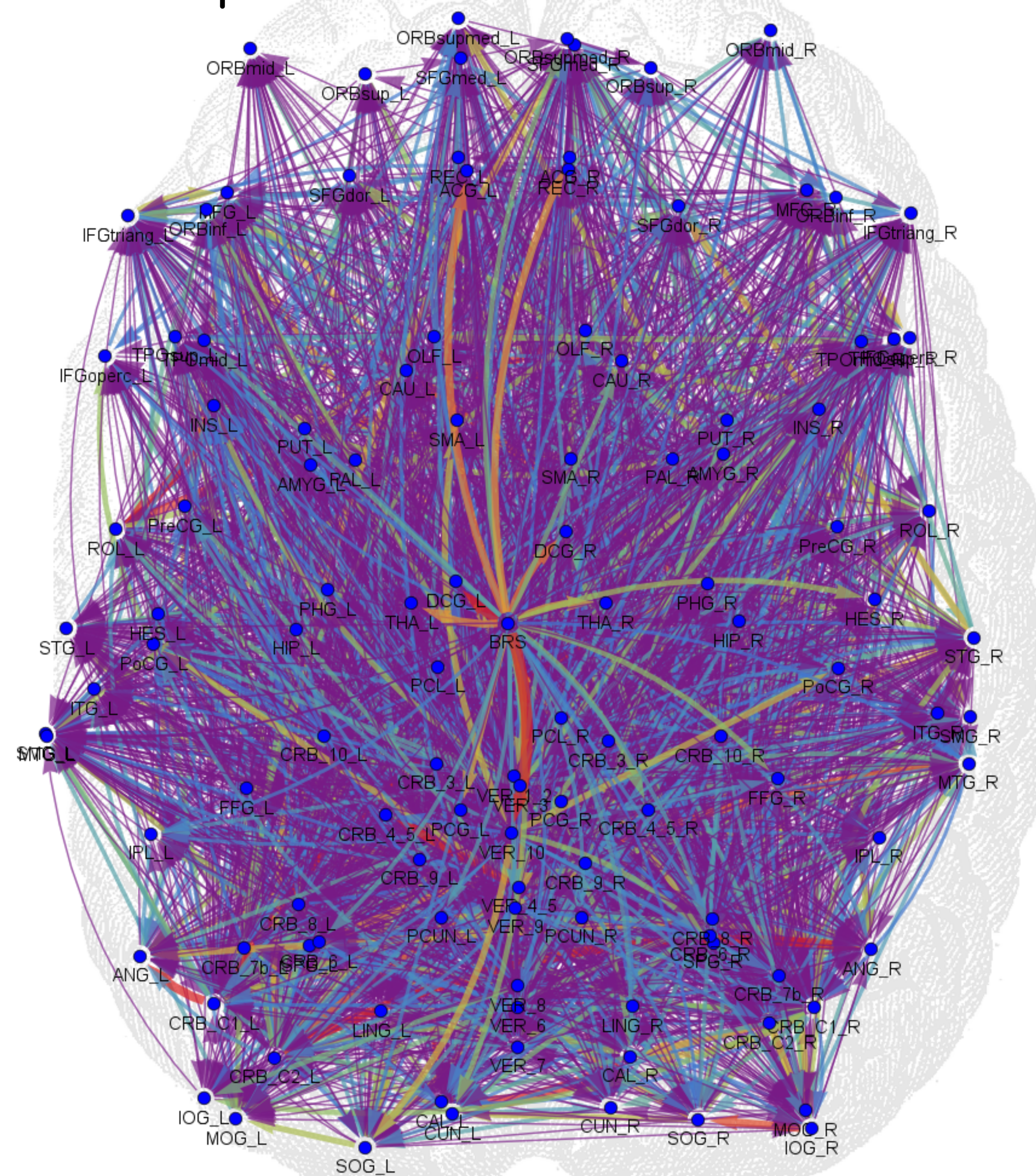

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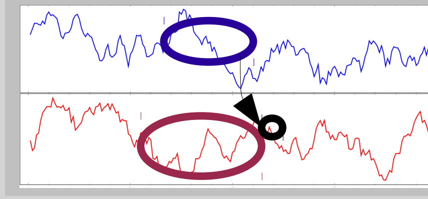

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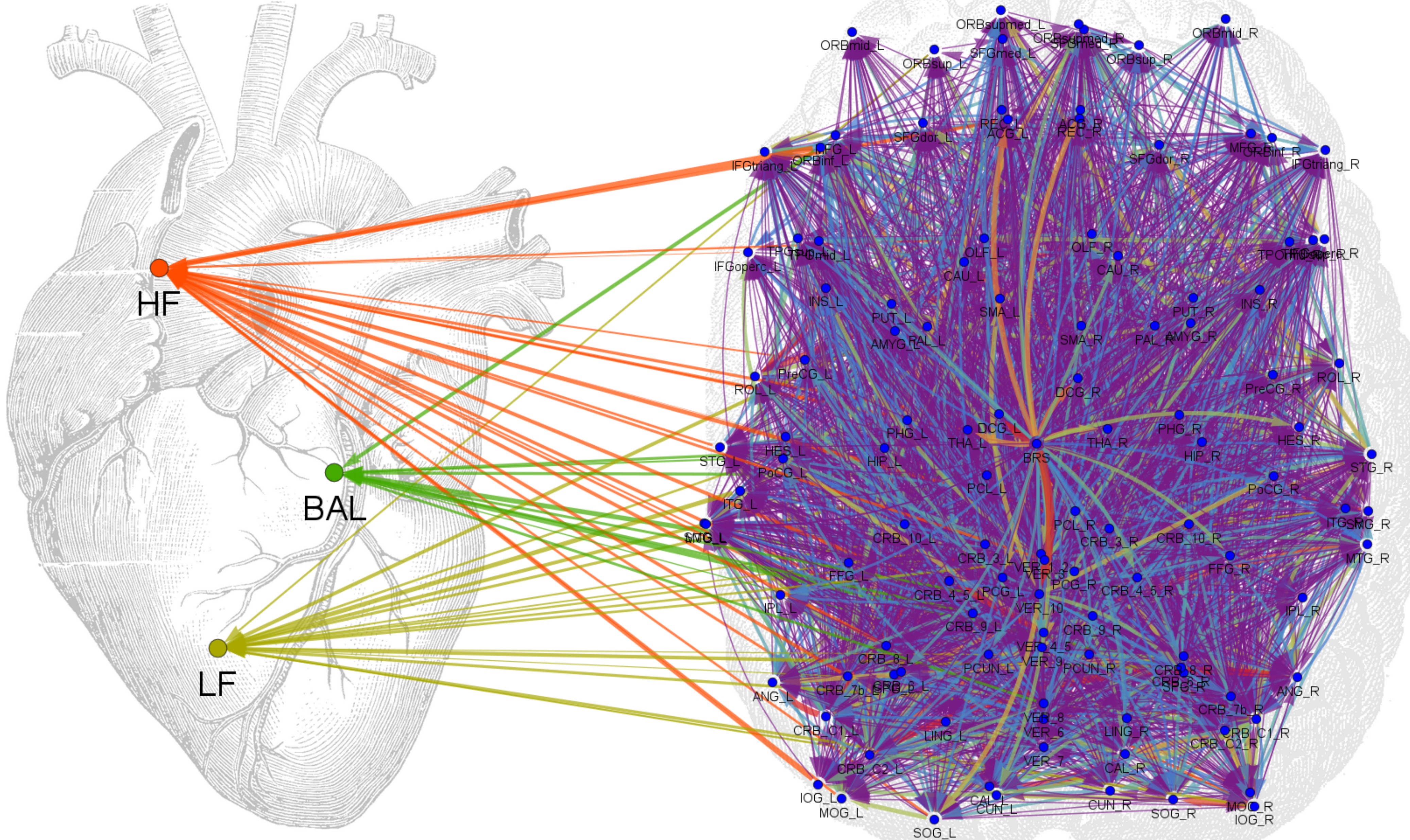

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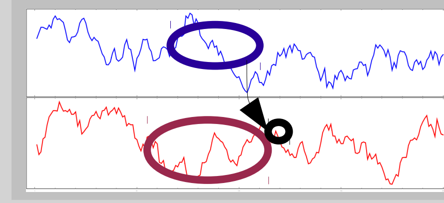

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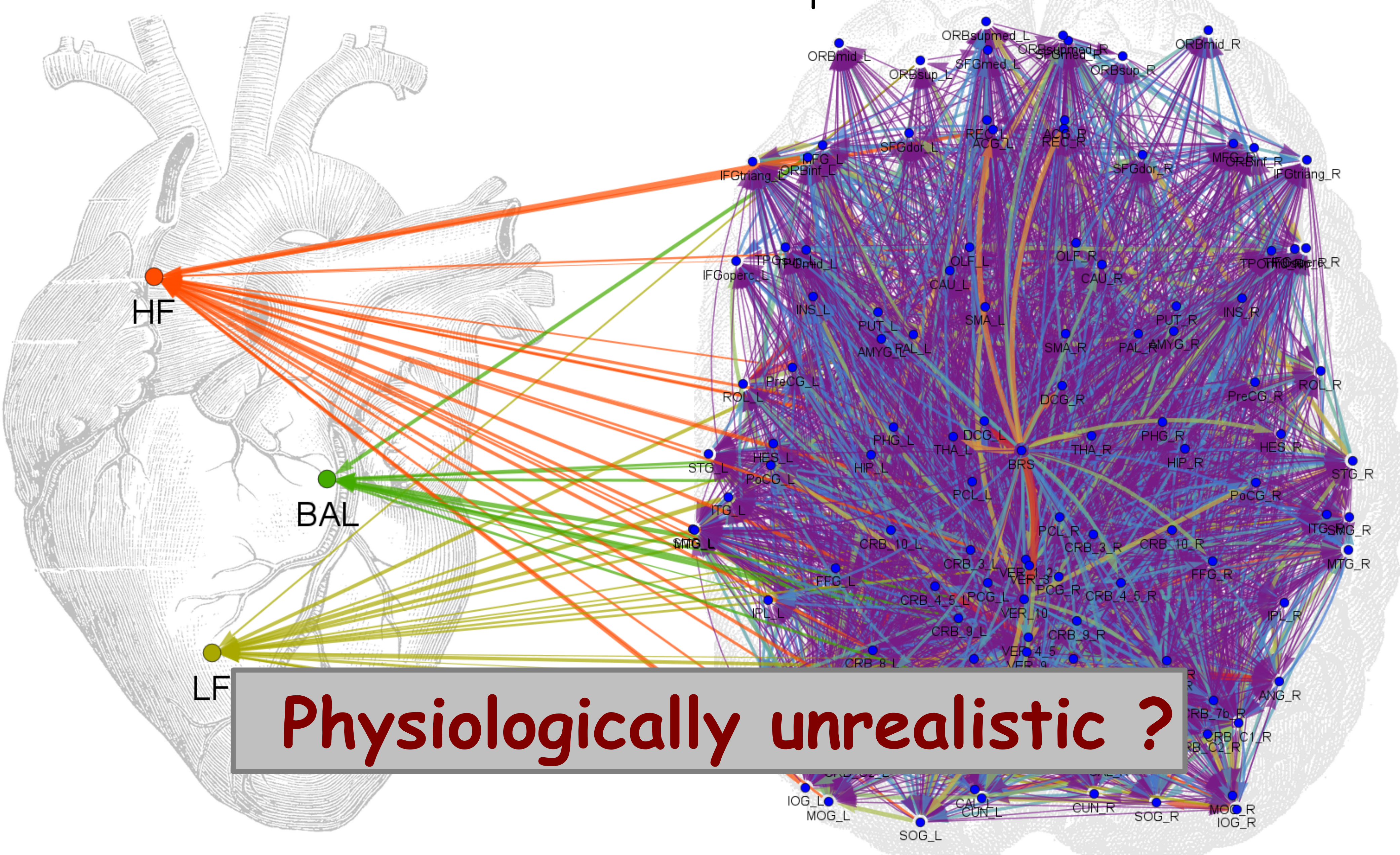
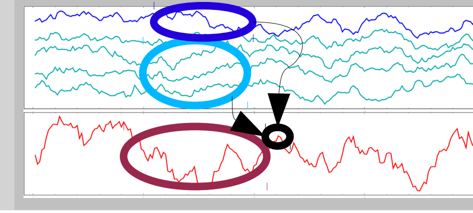
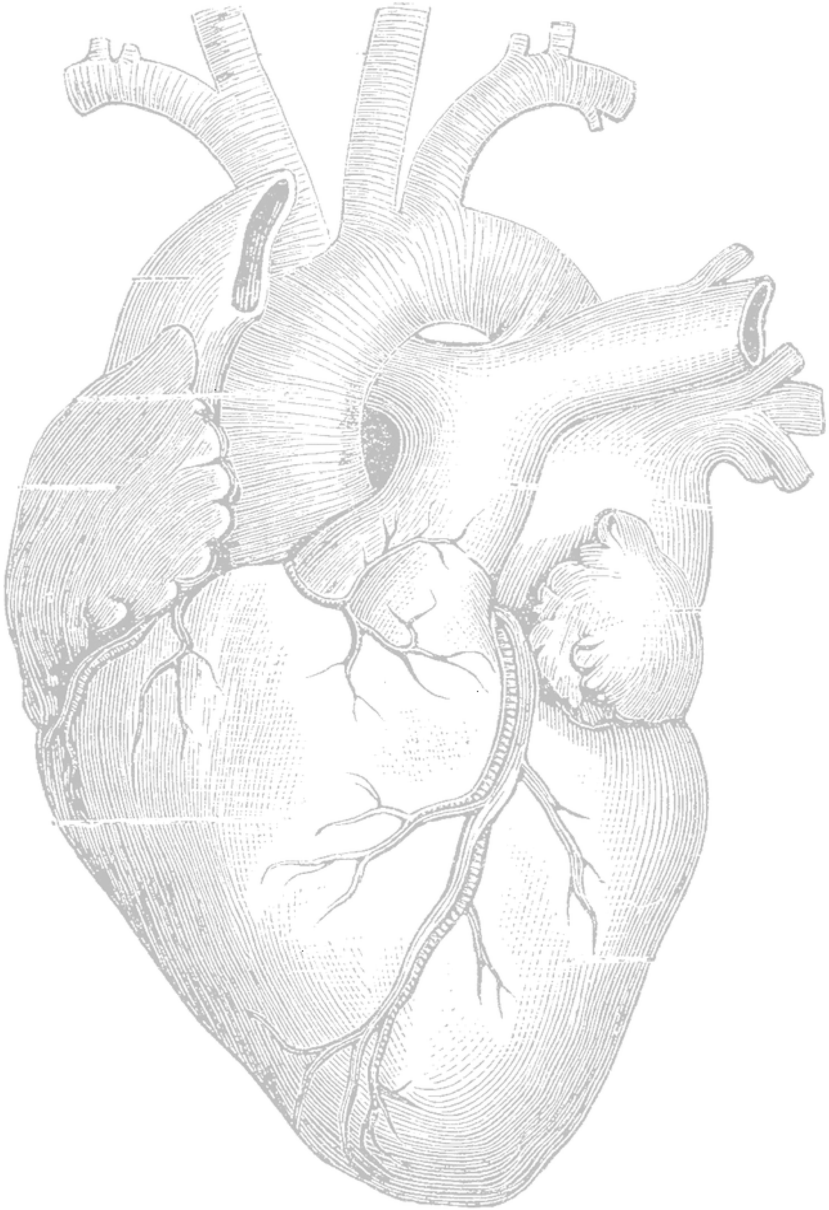


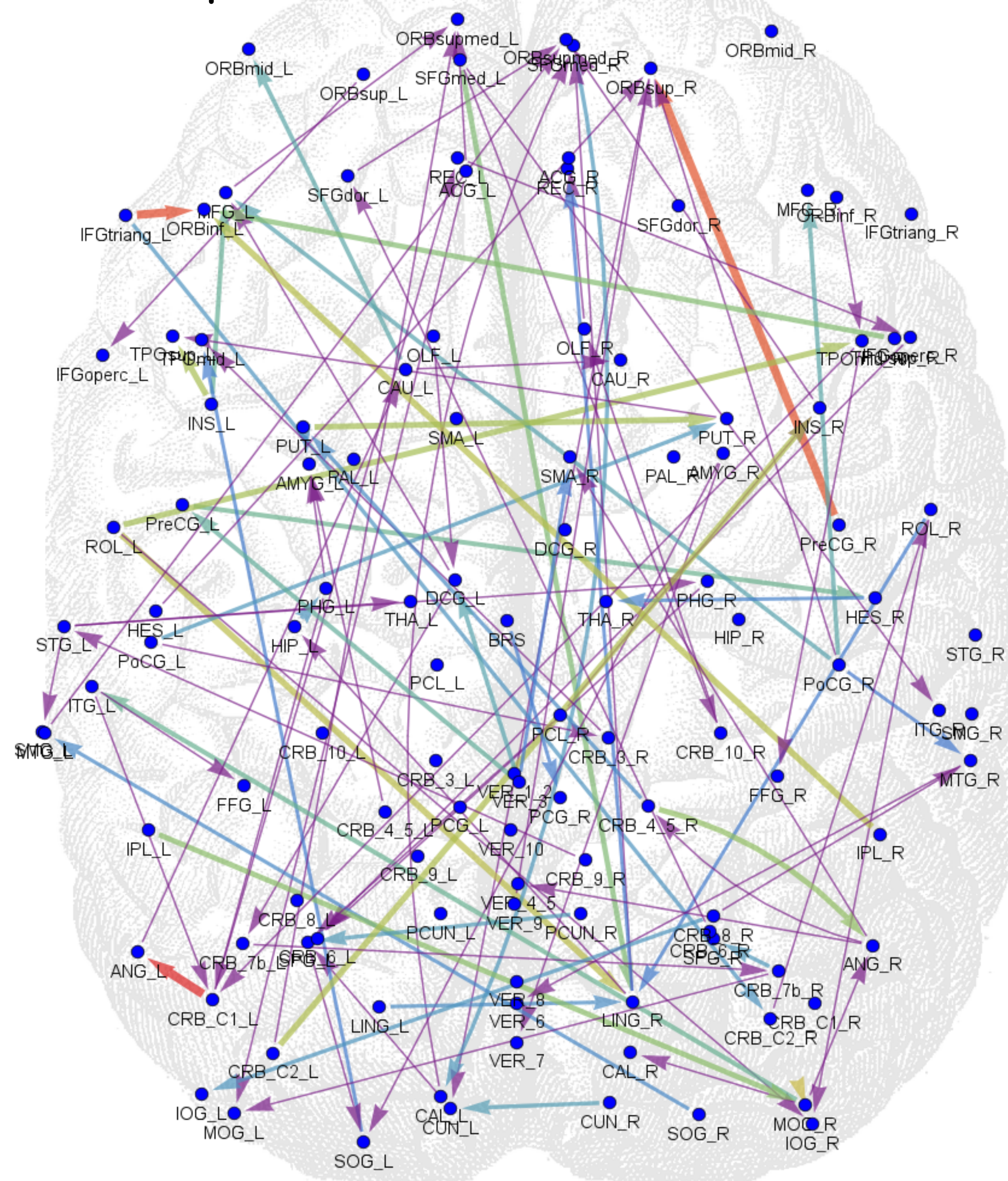
Physiologically unrealistic ?

Results - Globally conditioned GC





p-value based GCGC network



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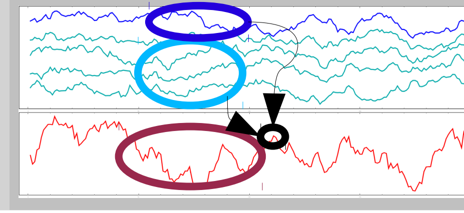

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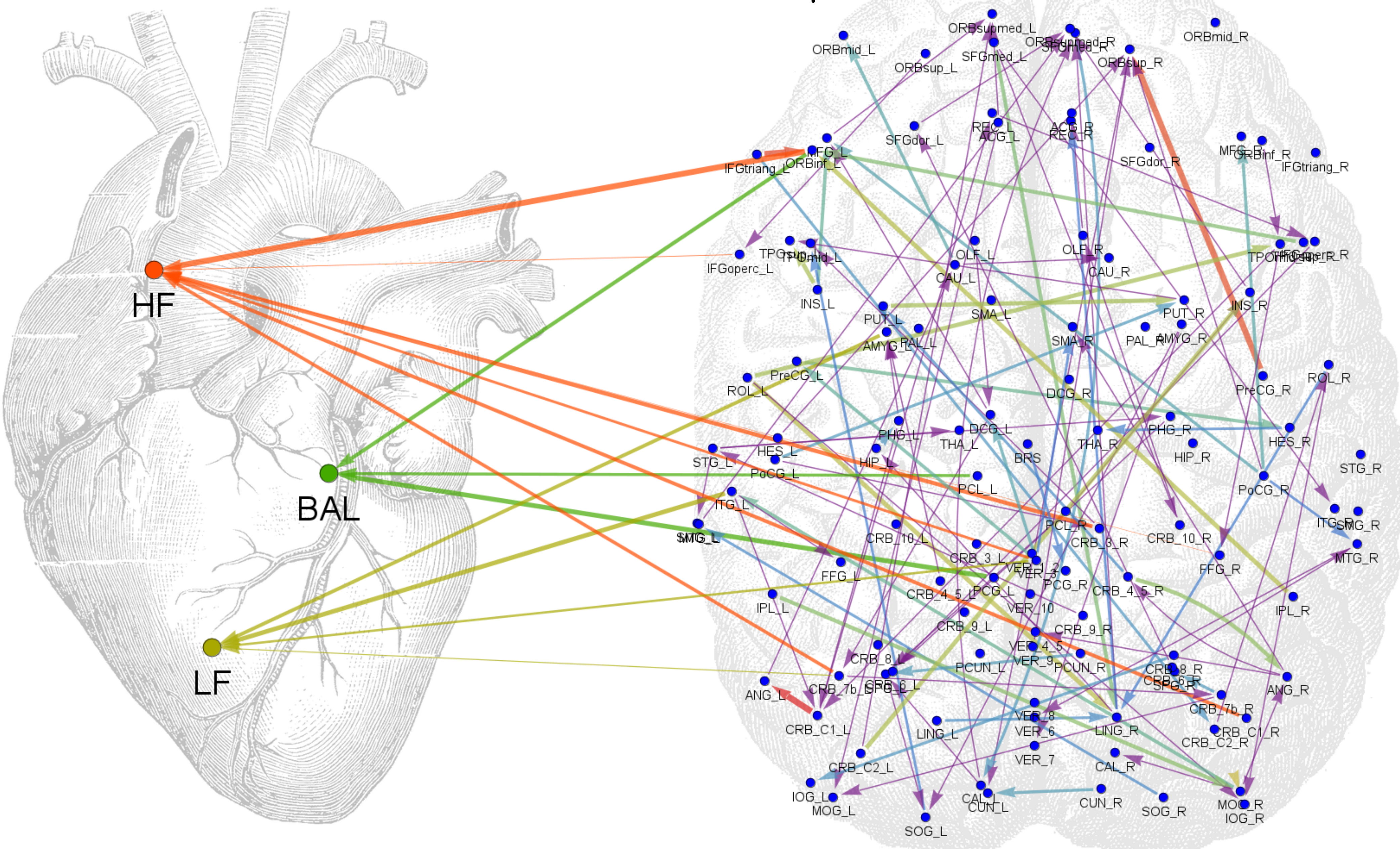

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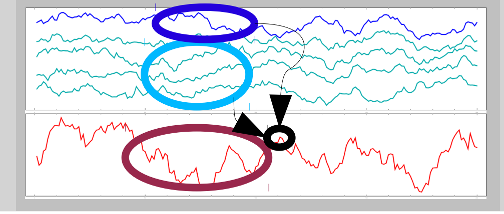

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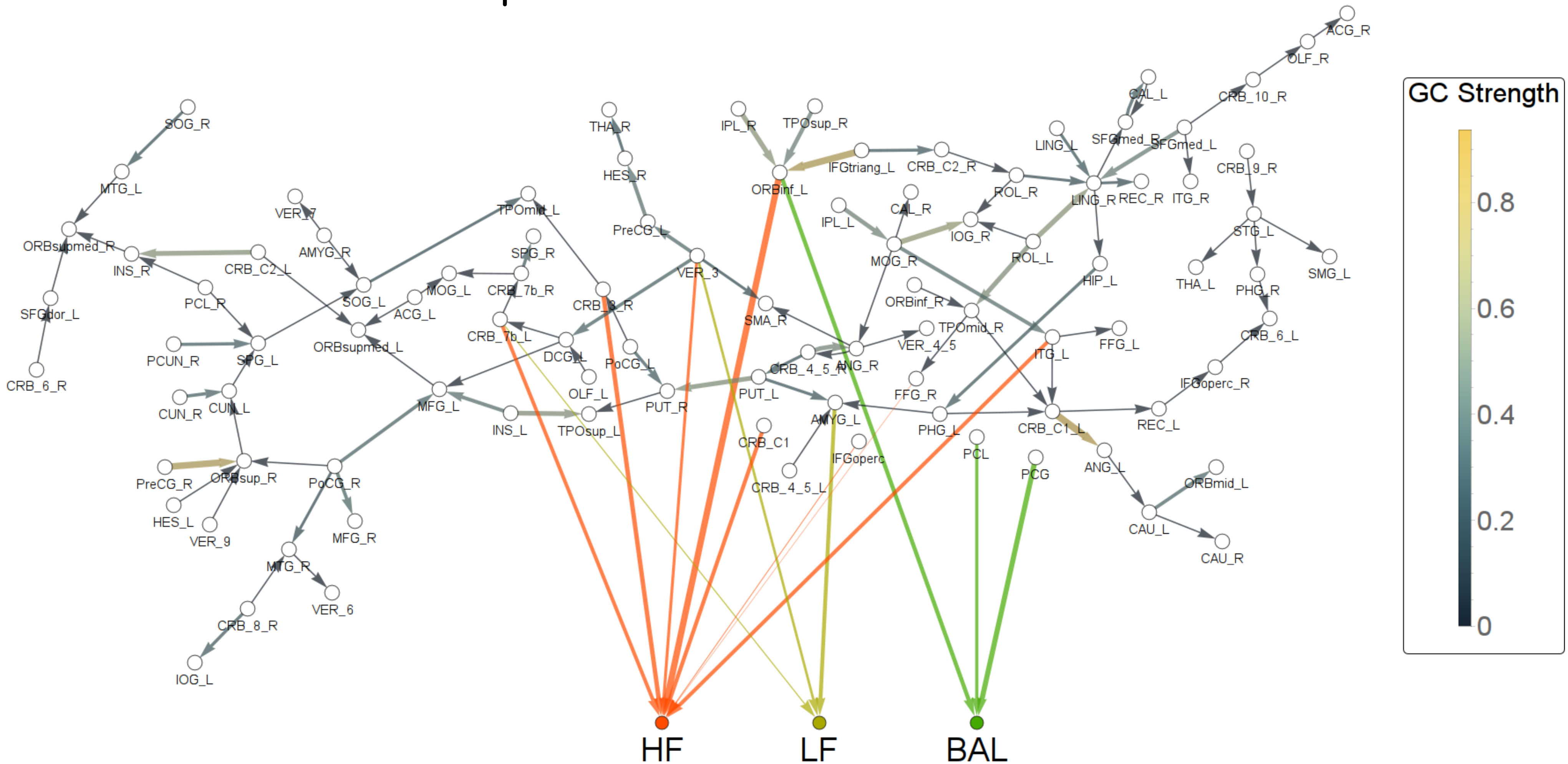

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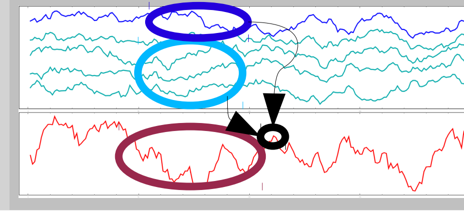

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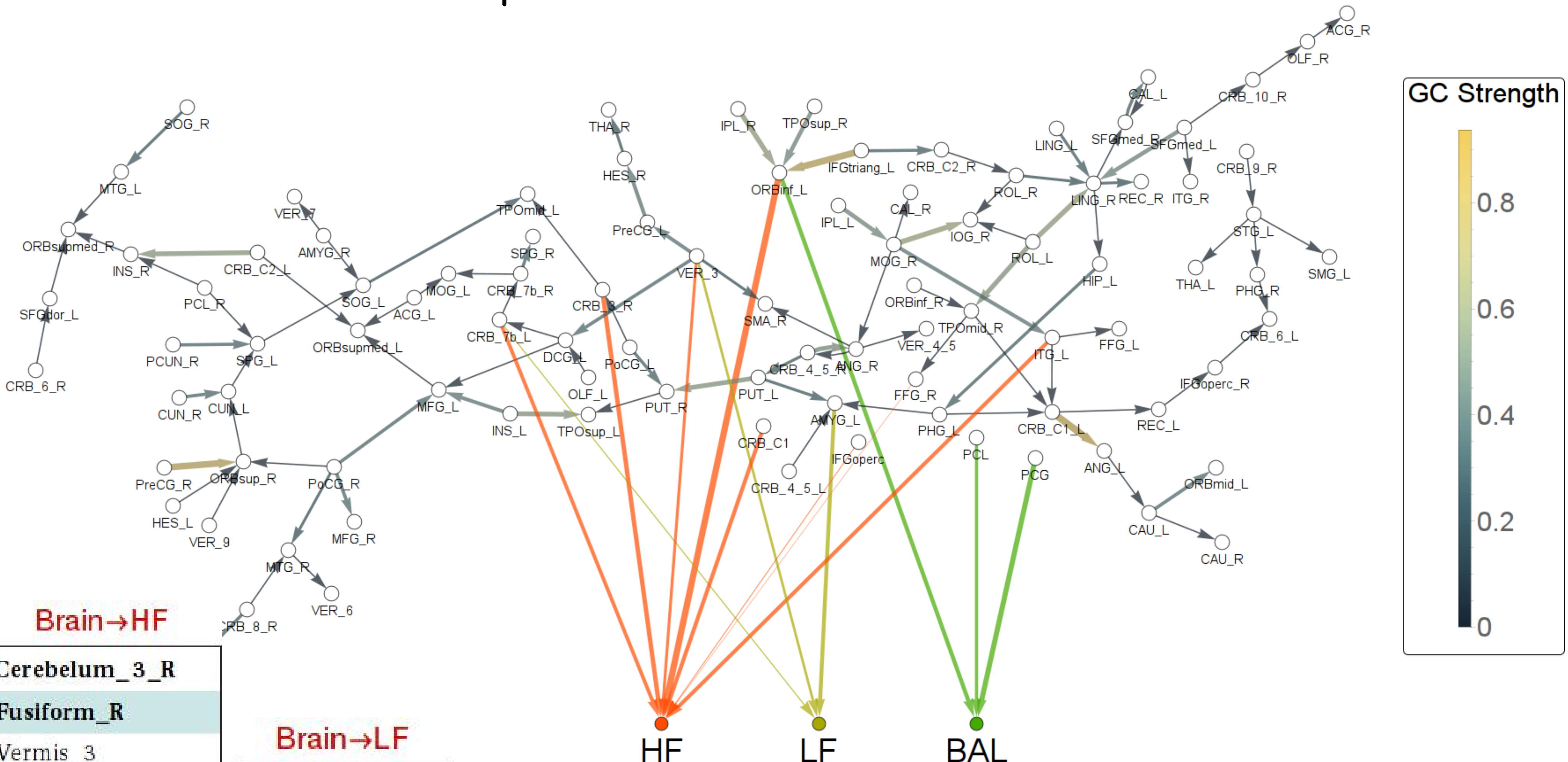

Brain→HF

Cerebelum_3_R
Fusiform_R
Vermis_3
Cerebelum_7b_L
Cerebelum_Crus1_R
Frontal_Inf_Orb_L
Frontal_Inf_Oper_L

Brain→LF

Cerebelum_7b_L
Temporal_Inf_L
Amygdala_L
Frontal_Inf_Tri_R

Brain→BAL

Paracentral_Lobule_L
Cingulum_Post_L
Frontal_Inf_Orb_L

Conclusions

- High SNR and SMS multiband **enable GC applications** in joint fMRI ANS studies
- Globally conditioned GC **successfully disentangles** high redundancy between locally aggregated brain signals.
- We show **novel, directed brain-heart interaction** which can be interpreted in terms of central modulation of ANS outflow

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Thank you!