Functional connectivity analysis : Application to motor skill learning in humans

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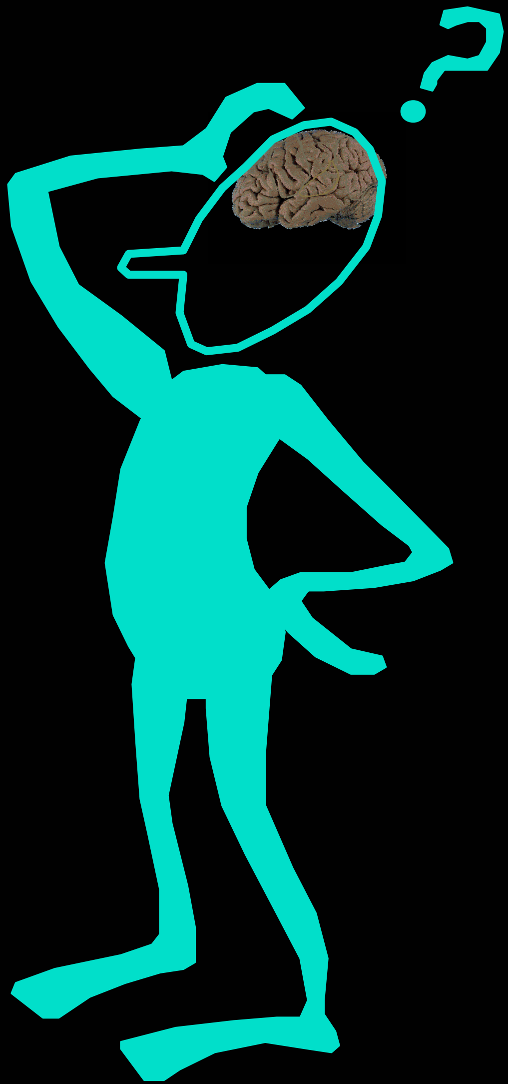
Functional connectivity

Concept of brain connectivity



Numerous definition of functional connectivity

- multiple types of data
- different spatial and temporal resolution
- functional interactivity differ from one another
- data represent neural ensemble activities
- data represent macroscopic brain regions
- different computational algorithms
- correlation within a task
- correlation between task

Lack of definition of functional connectivity

- the relationship between the defined functional connectivity and its underlying neural substrate is unknown
- concept of functional connectivity is not well defined

B. Horwitz, NeuroImage, 19, 2003

Functional connectivity : definition

Friston's definition

•Functional connectivity is defined as the temporal correlation between spatially defined brain regions

•Effective connectivity is defined as the influence that one brain region exerts on another.

Other definition (Aertsen and Preissl, 1991)

Functional connectivity is defined as a groups of neurons that act together in a coherent fashion

Functional connectivity : definition

Brain connectivity

• Brain unit can be thought of as the amount of brain tissue giving rise to the activity recorded in a single time series. Each unit is then associated to a *functional process*, or phenomenon, that characterizes it.

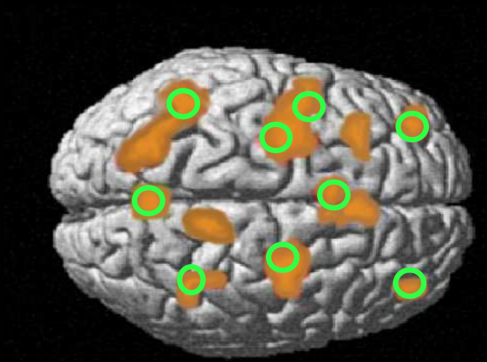
Exemple: In fMRI, they can be thought of as the BOLD contrast measured at a particular time sample.

• Functional brain interactivity be defined as *all potential or real information exchanges between brain units*

Marrelec G et al. IEEE TSP 2005

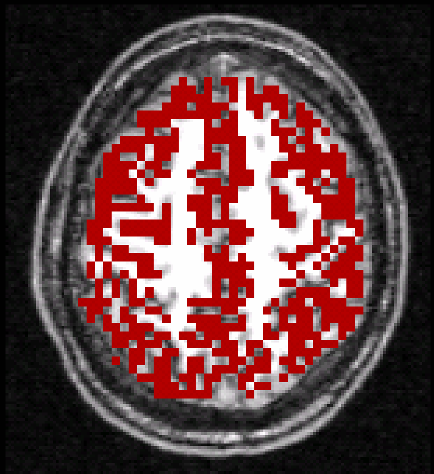
Functional connectivity

Brain unit



Brain units : Competitive region growing algorithm

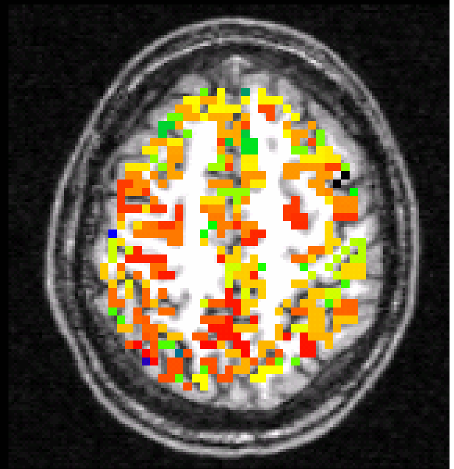
Hypothesis : Brain regions considered for functional connectivity purpose must be composed of voxels having an homogeneous temporal signal.



Cerebral cortex

Competitive region growing algorithm:

1. Initially, clusters are all singletons.
2. Similarity measure between clusters: mean correlation over all pairs of voxels
3. Clusters are merged if they are MNN, with respect to 26-connexity, similarity measure, extent of the merged cluster < p voxels.
4. Algorithm stops when no more merging is possible.

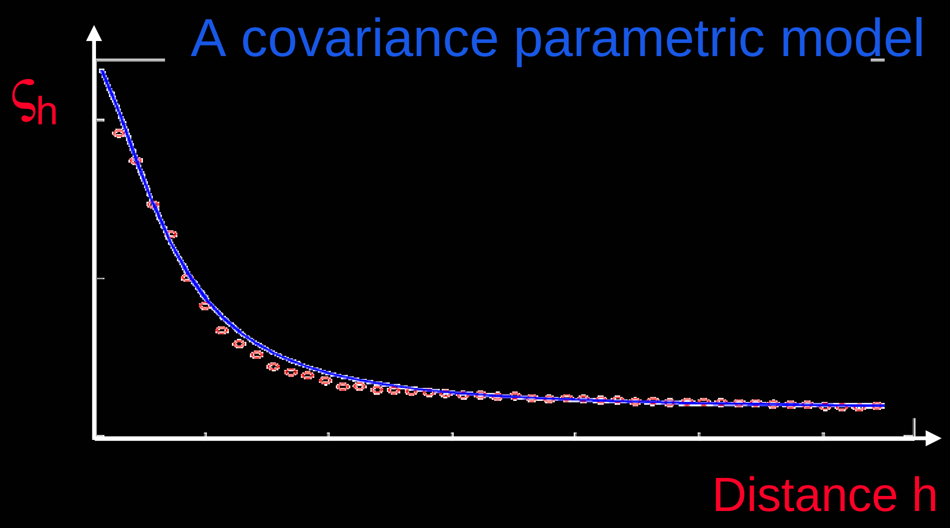


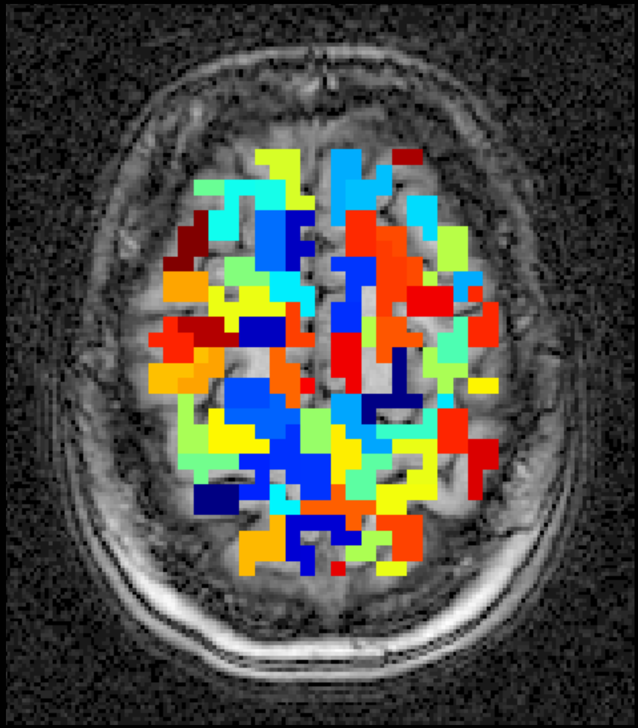
Homogeneous brain areas

Bellec et al. *ISBI* (2004)

Brain unit in fMRI

Hypothesis: Noise in fMRI data is spatially correlated. Appropriate tests on functional connectivity must take it into account.



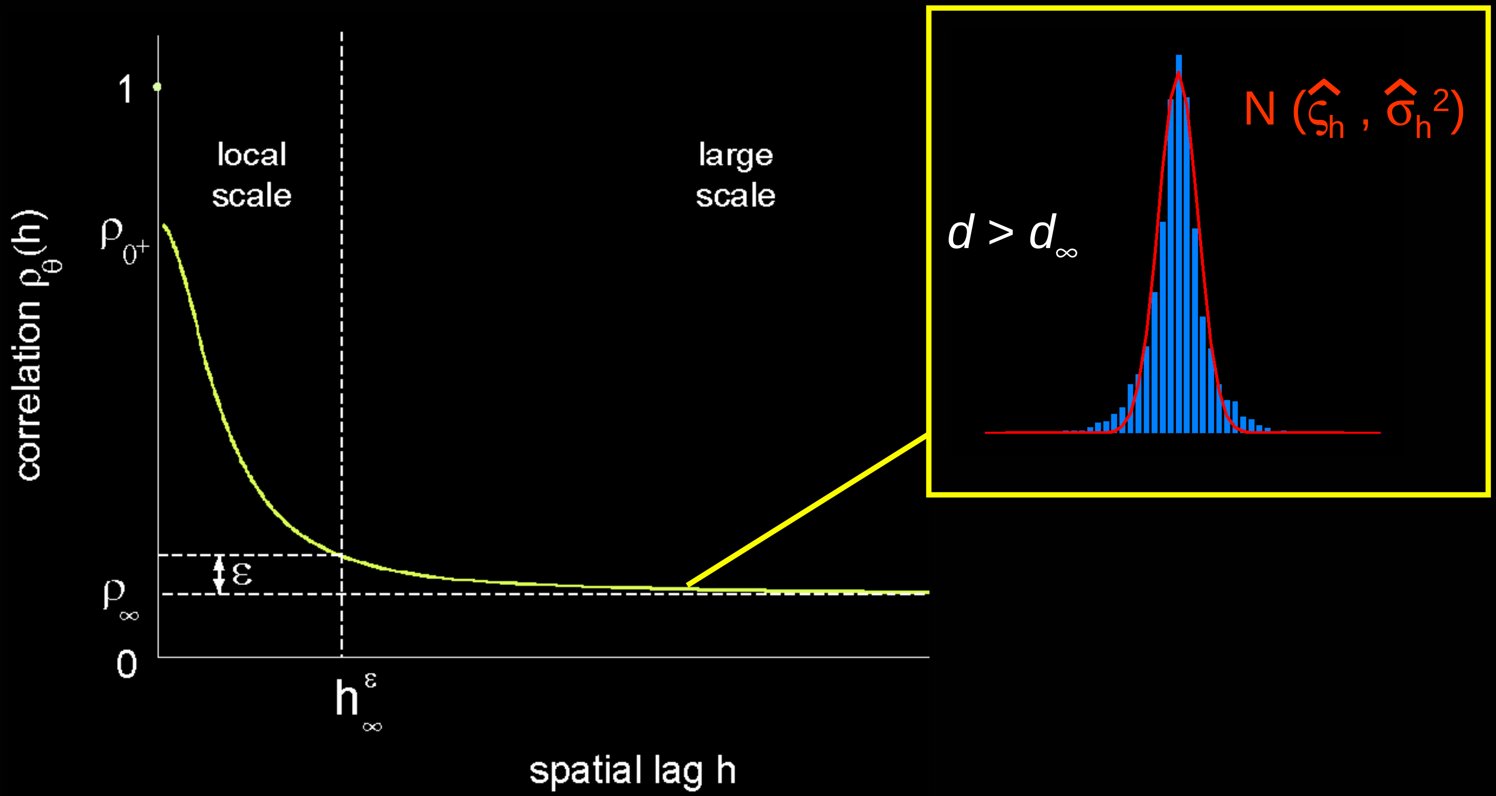


Rational-quadratic model of the covariance is a function of the distance between clusters

Bellec et al. (2004) *ISBI*

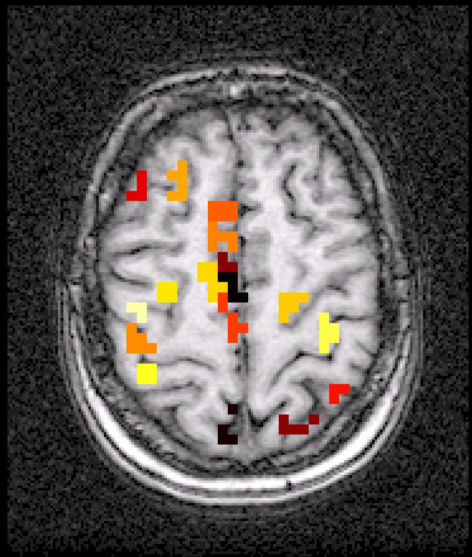
Brain unit in fMRI

Hypothesis : As spatially close regions may correlate only due to spatial proximity, we wish to detect regions exhibiting functional connectivity with distant regions.



$$\sqrt{v}\mathcal{L} \sim \mathcal{N}(\mu, D)$$

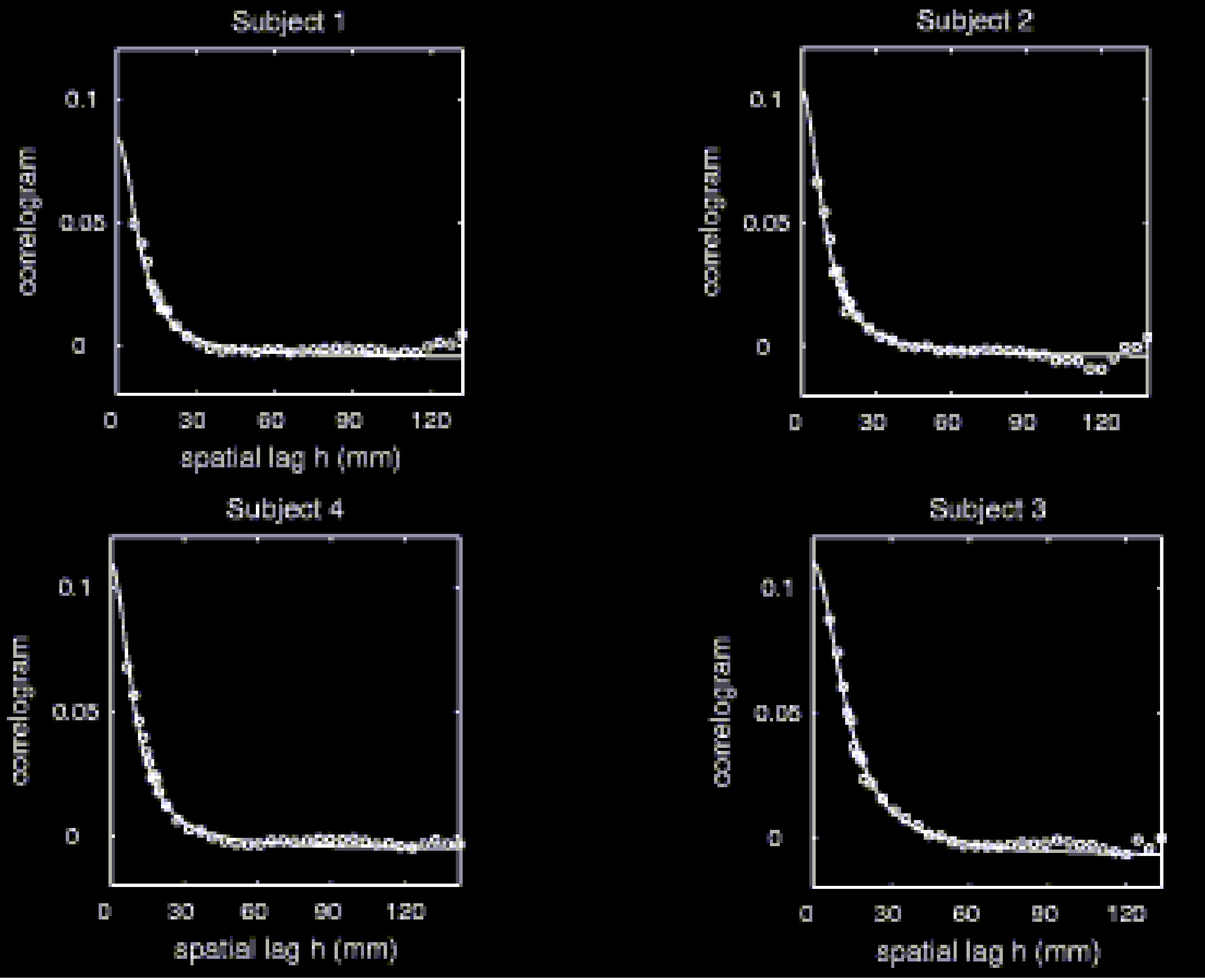
$$\mu_{ij} = \rho_\infty \qquad D_{ij,kl} = \rho_\infty^2 + \rho_{0^-}^2$$



Identified large-scale functional brain units

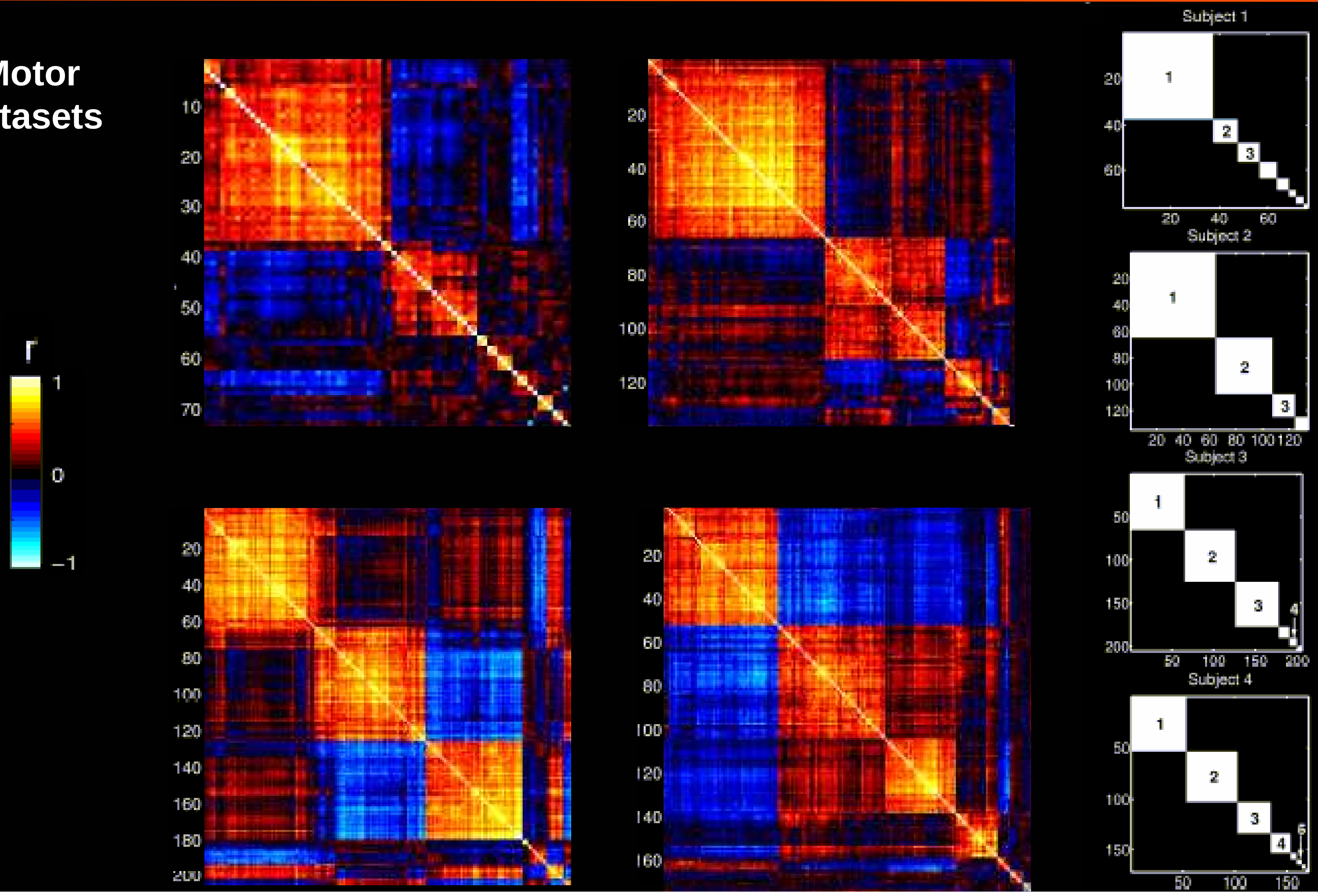
Bellec et al. *NeuroImage (2005)*

Brain unit in fMRI

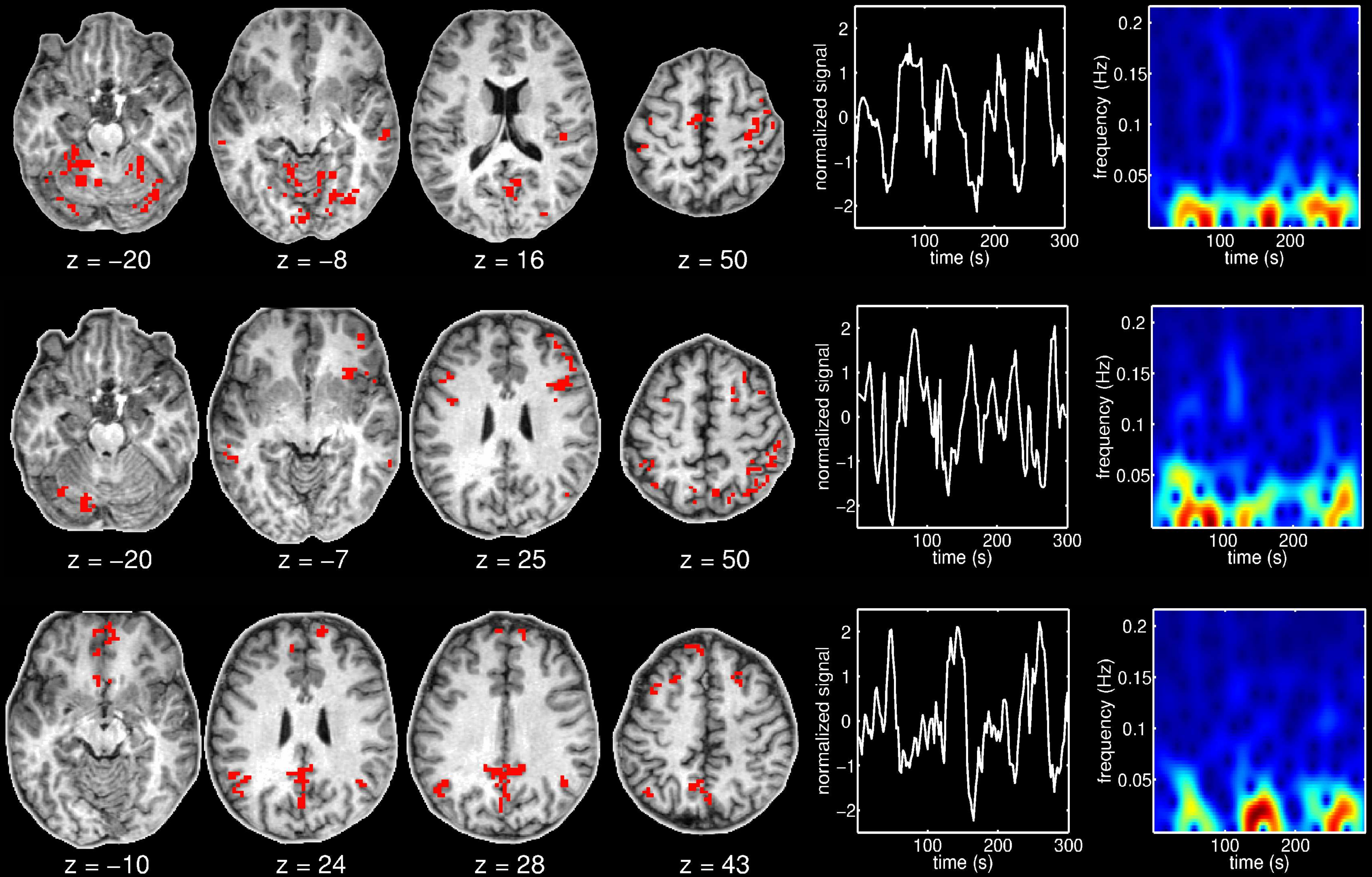


Identification of a large-scale functional network in fMRI

Motor datasets



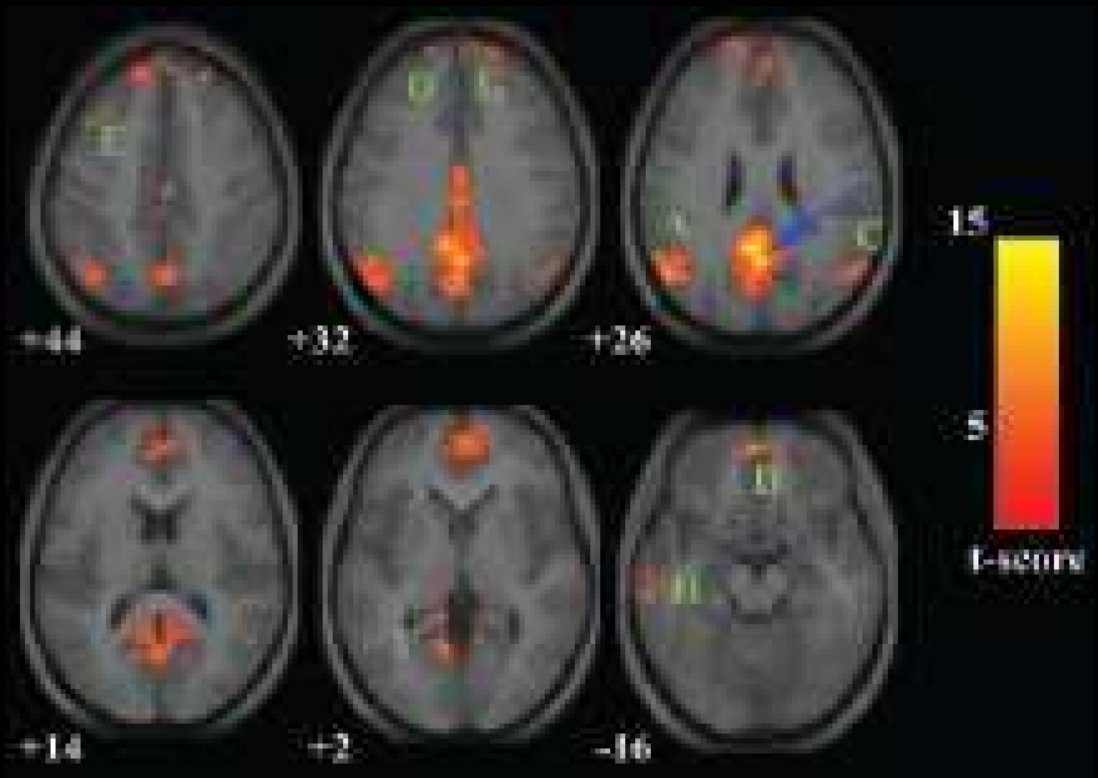
Identification of a large-scale functional network: motor task



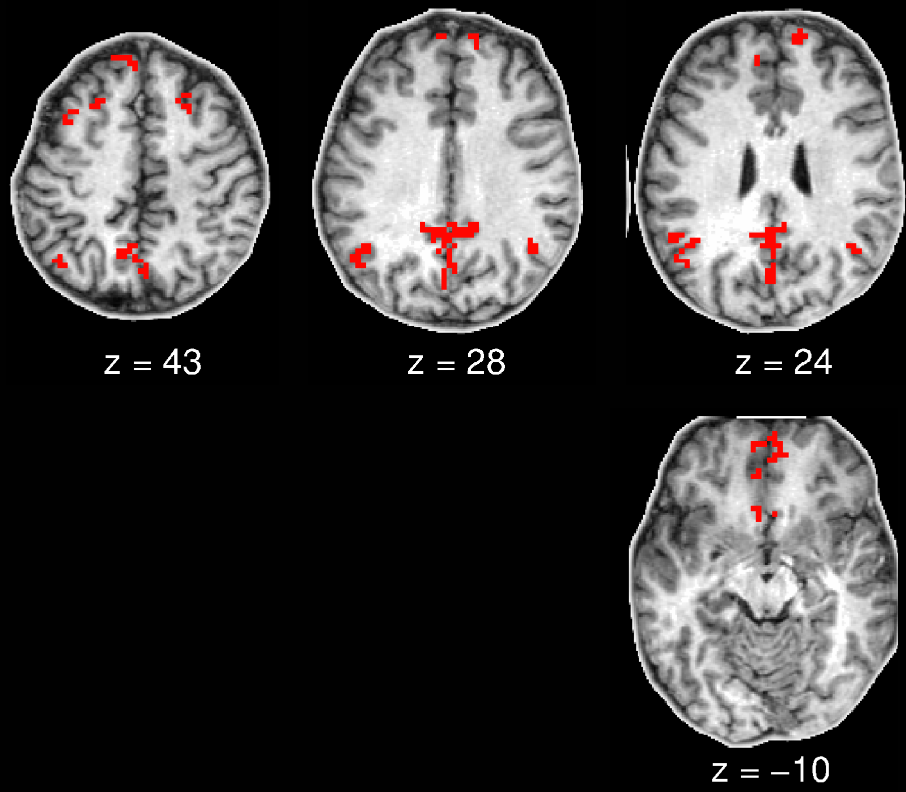
Bellec et al. Neuroimage 2005

Identification of a large-scale functional network: default mode hypothesis

Functional connectivity in the resting brain : A network analysis of the default mode hypothesis. Creicius et al. PNAS, 2003, 2004.

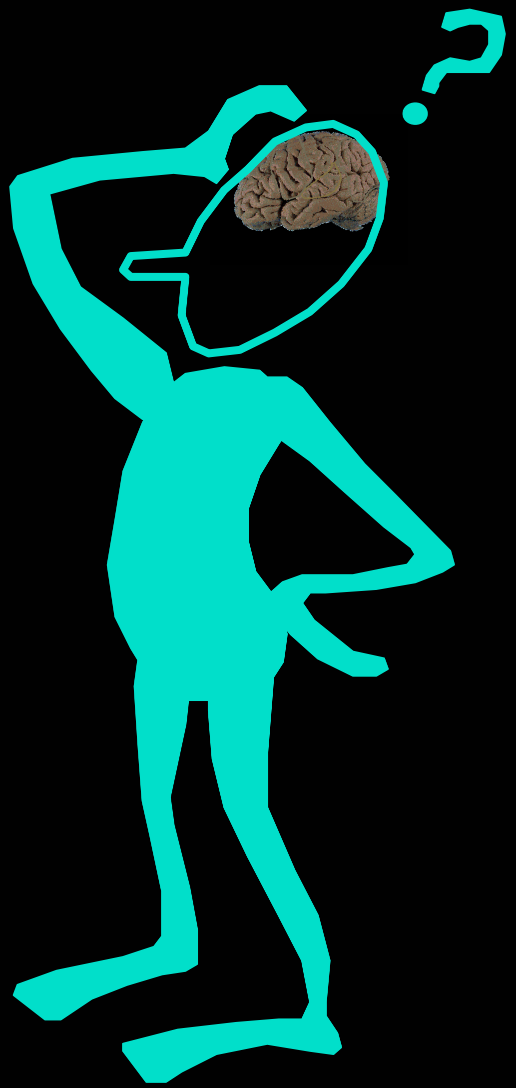


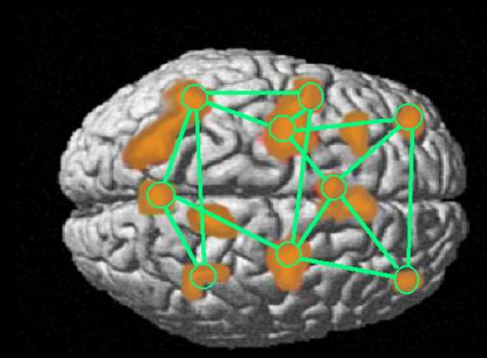
ISNI model. Bellec et al. Neuroimage, 2005



Functional brain interactivity

Functional connectivity





Functional brain interactivity : non-linear correlation

Non linear correlation coefficient

$$h_{ij}^{2*} = \max_{\tau} h_{ij}^2(\tau).$$

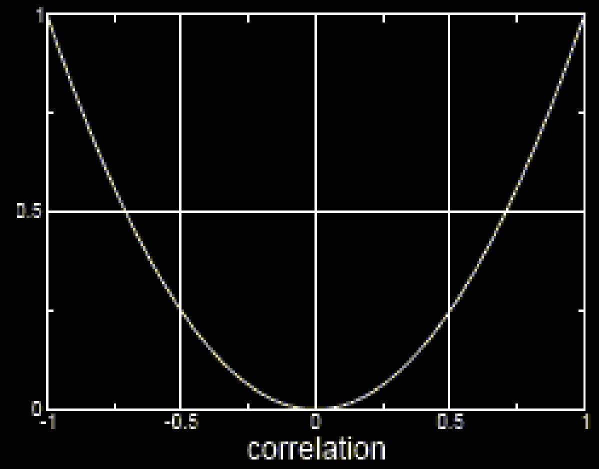
$$h_{ij}^2(\tau) = 1 - \frac{\mathrm{Var}[Y_j(t+\tau) - h_{\hat{\theta}_{ij}(\tau)}(Y_i(t))]}{\mathrm{Var}[Y_j(t+\tau)]}.$$

$$\hat{\theta}_{ij}(\tau) = \arg\min_{\boldsymbol{\theta}} \mathrm{E}\left[(Y_j(t+\tau) - h_{\boldsymbol{\theta}}(Y_i(t)))^2\right]$$

i.i.d Gaussian process (μ , Σ)

$$h_{\boldsymbol{\theta}}(y) = \mu_j + a + b(y - \mu_i)$$

$$\boxed{h_{ij}^{2*} = \rho_{ij}^2}$$



Marrelec et al. IEEE TSP 2005

Functional brain interactivity : mutual information

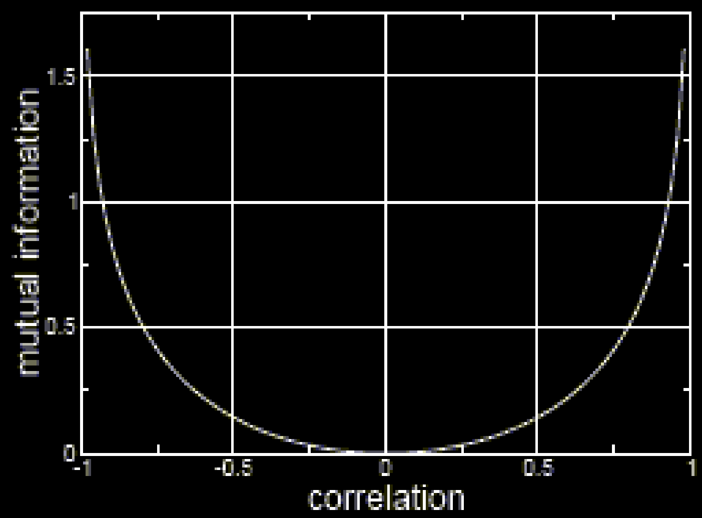
Mutual information

$$\mathrm{MI}_{ij} = H(Y_i(t)) + H(Y_j(t)) - H(Y_i(t), Y_j(t))$$

$$H(X) = -\int \Pr(X) \cdot \ln \Pr(X) \, \mathrm{d}X$$

i.i.d Gaussian process (μ , Σ)

$$\mathrm{MI}_{ij} = -\frac{1}{2} \ln \left(1 - \rho_{ij}^2\right)$$



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Functional brain interactivity : Phase synchronization and PLV

Phase synchronization

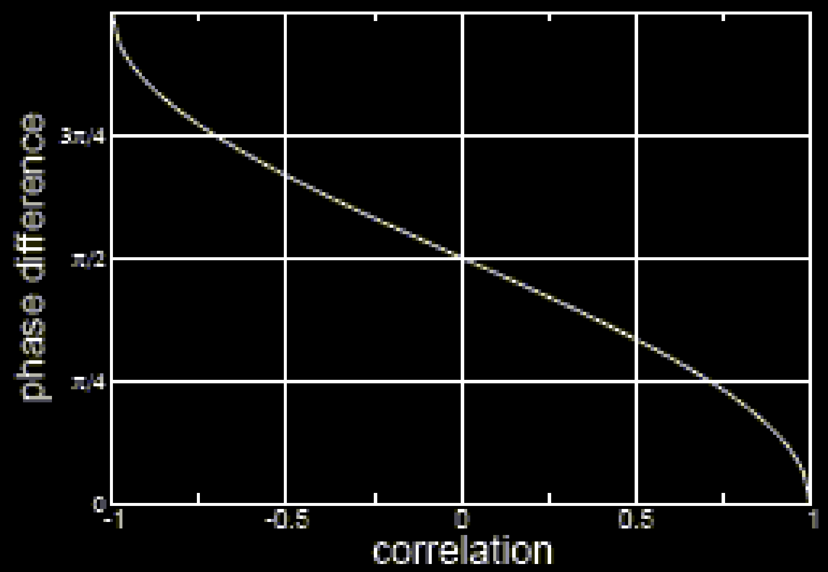
$$Y_n(t) = a_n \cos(2\pi\nu_n t + \phi_n)$$

$$\psi_{ij} = \phi_i - \phi_j$$

$$\psi_{ij} = \arccos(\rho_{ij})$$

$$\begin{aligned} \mathrm{E}[\psi_{ij}] &= \int \psi_{ij} \cdot f(\psi_{ij})\, \mathrm{d}\psi_{ij} \\ &= \int \arccos(\rho_{ij}) \cdot g(\rho_{ij})\, \mathrm{d}\rho_{ij} \end{aligned}$$

i.i.d Gaussian process (μ , Σ)



Phase Looking Value

$$\gamma_{ij}^2(\nu) = \frac{\left| \frac{1}{E} \sum_{e=1}^{E} S_{i,e}(\nu) S_{j,e}(\nu)^* \right|^2}{\left[\frac{1}{E} \sum_{e=1}^{E} S_{i,e}(\nu) S_{i,e}(\nu)^* \right]^2 \left[\frac{1}{E} \sum_{e=1}^{E} S_{j,e}(\nu) S_{j,e}(\nu)^* \right]^2}$$

$$\gamma_{ij}^2(\nu) = \left[\int \cos(\psi_{ij}) \cdot f(\psi_{ij})\, \mathrm{d}\psi_{ij} \right]^2 + \left[\int \sin(\psi_{ij}) \cdot f(\psi_{ij})\, \mathrm{d}\psi_{ij} \right]^2$$

Functional brain interactivity : Generalized synchronization

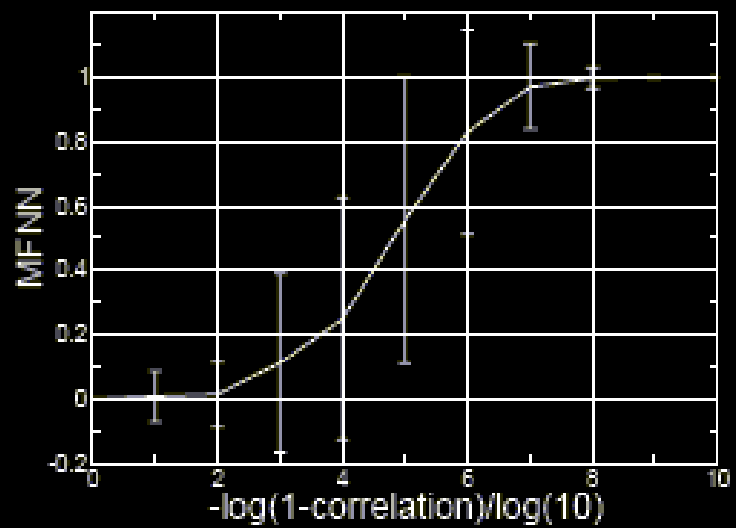
Generalized synchronization

$$\mathrm{MFNN}_{ij} = \frac{|Y_i(t) - Y_i(\tau_{i,t})|}{|Y_j(t) - Y_j(\tau_{i,t})|} \cdot \frac{|Y_j(t) - Y_j(\tau_{j,t})|}{|Y_i(t) - Y_i(\tau_{j,t})|}$$

$$\tau_{n,t} = \arg\min_u |Y_n(t) - Y_n(u)|$$

i.i.d Gaussian process (μ , Σ)

$$\Sigma = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$$



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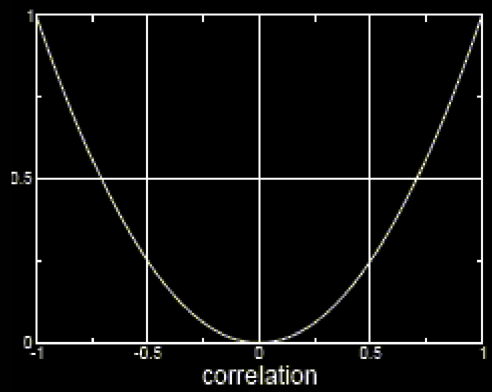
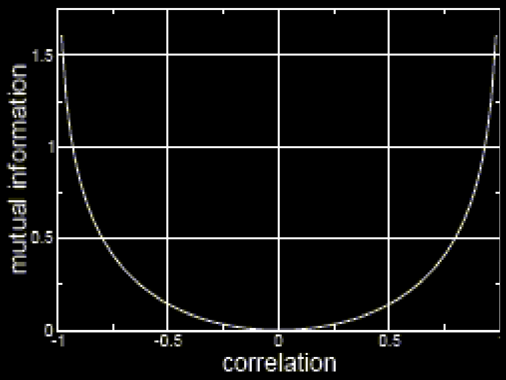
Functional brain interactivity : summary

Hypothesis: Y i.i.d multivariate Gaussian, with mean μ and covariance matrix Σ

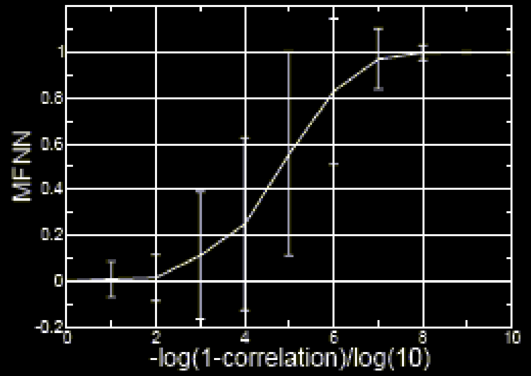
Non linear correlation



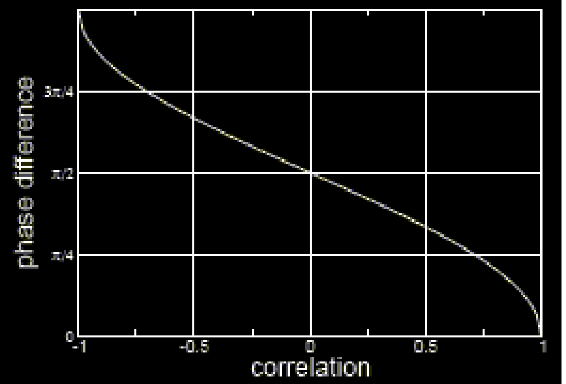
Mutual information



Generalized synchrony



Phase difference



measure of interaction	expression	no interaction	maximum interaction
correlation	$\mathrm{Corr}[Y_i, Y_j] = \rho_{ij}$	0	± 1
nonlinear correlation	$h_{ij}^{2*} = \rho_{ij}^2$	0	1
mutual information	$\mathrm{MI}_{ij} = -\frac{1}{2}\ln\left(1-\rho_{ij}^2\right)$	0	$+\infty$
generalized synchronization	?	0 or $+\infty$	1
phase difference	$\psi_{ij} = \arccos(\rho_{ij})$	$\pi/2 + k\pi$	$0 + k\pi$

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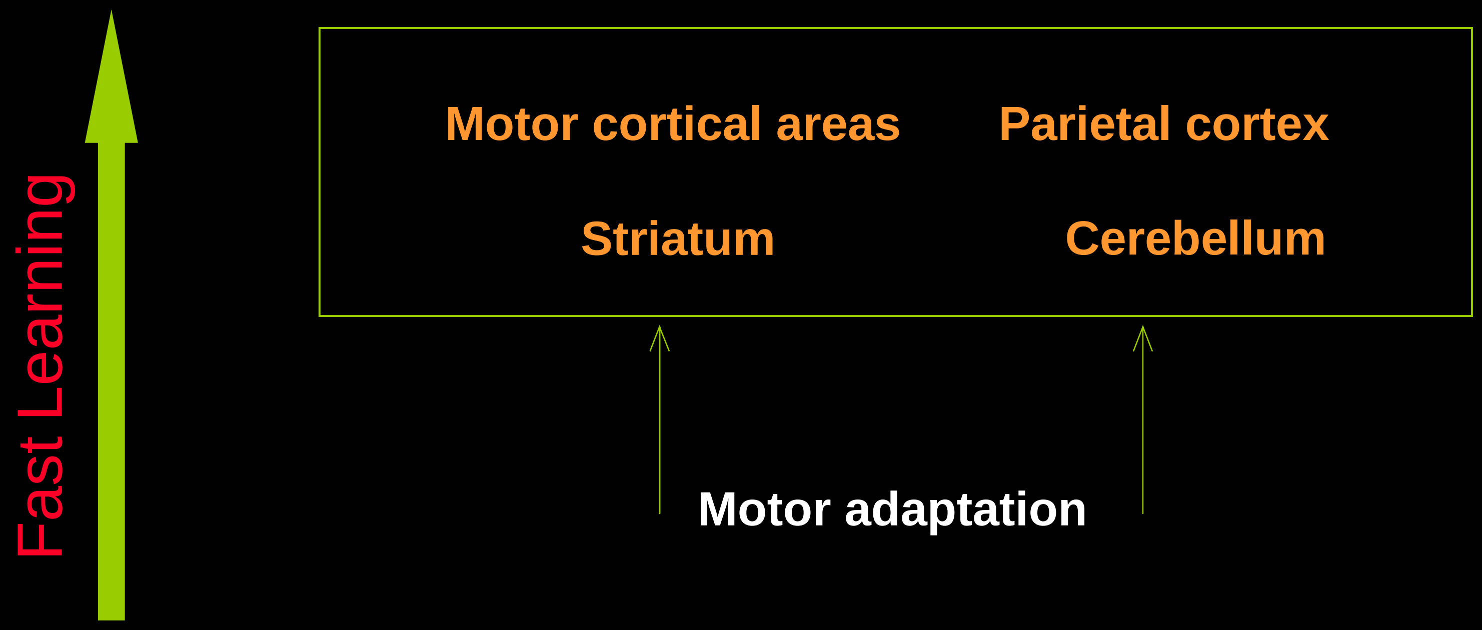
Functional network : cognitive model

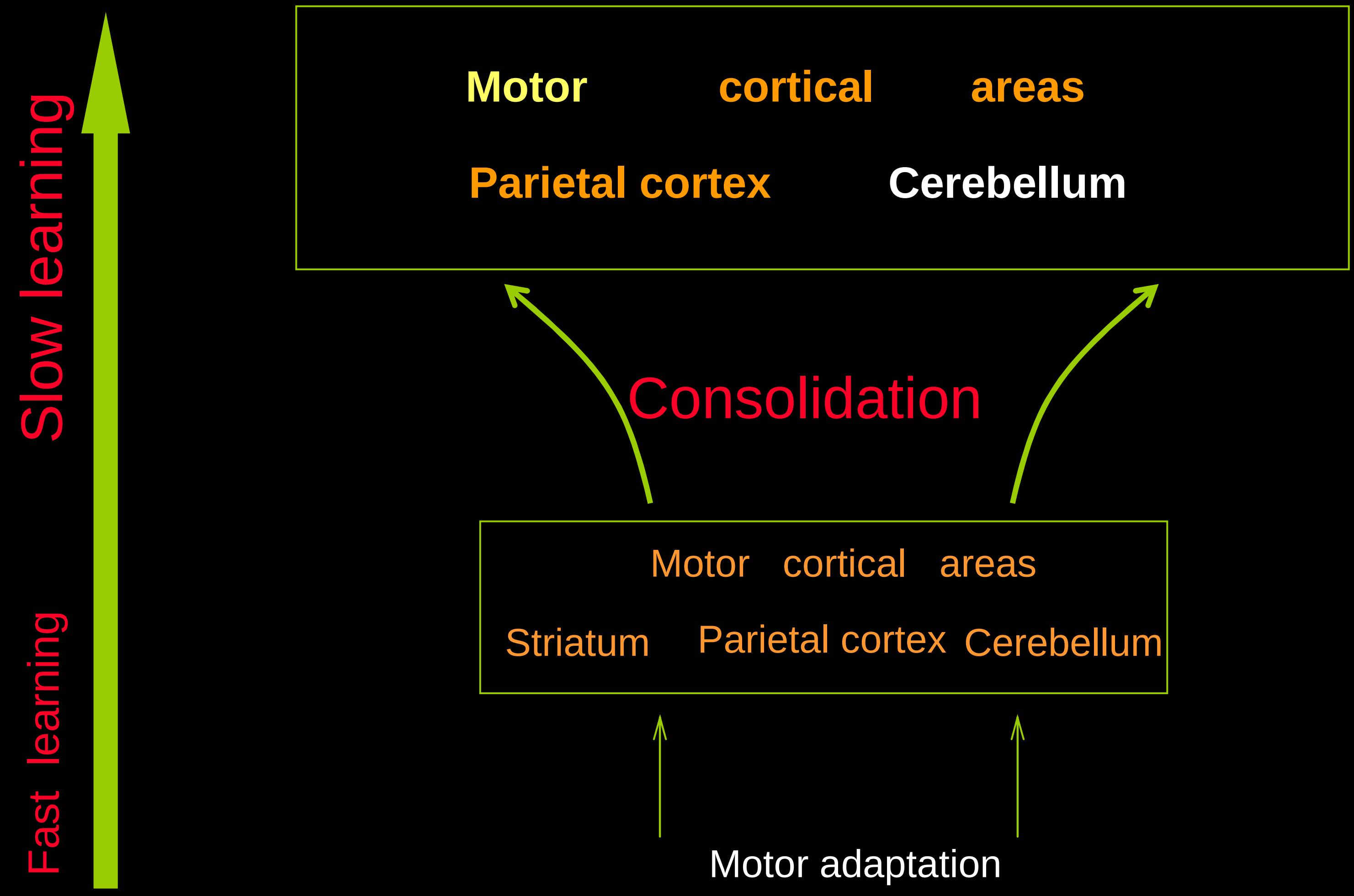
J. Doyon and L. Ungerleider's model



Doyon & Ungerleider (2002), Neuropsychology of Memory, 3nd Edition

Functional network : cognitive model

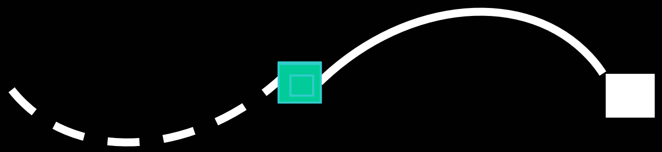
J. Doyon and L. Ungerleider's model

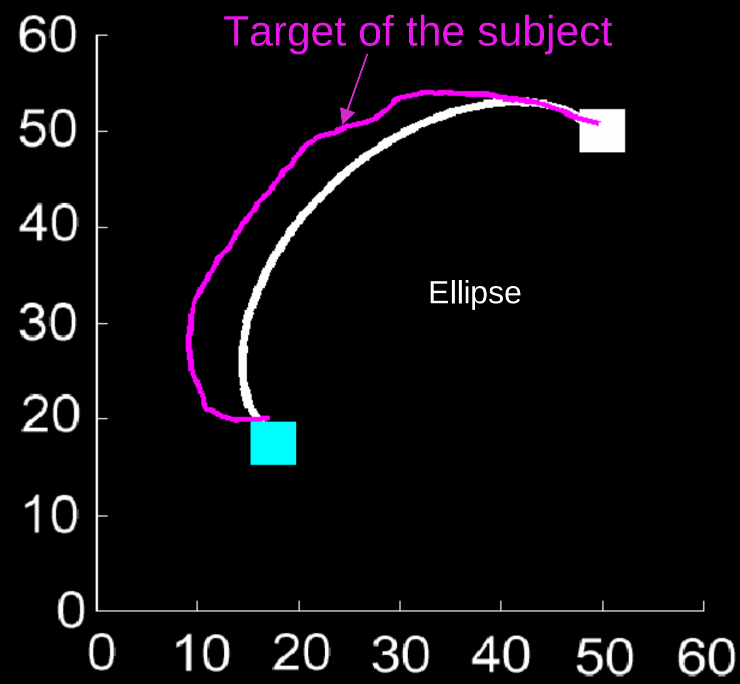


Doyon & Ungerleider (2002), Neuropsychology of Memory, 3rd Edition

Functional network : visuomotor adaptation task

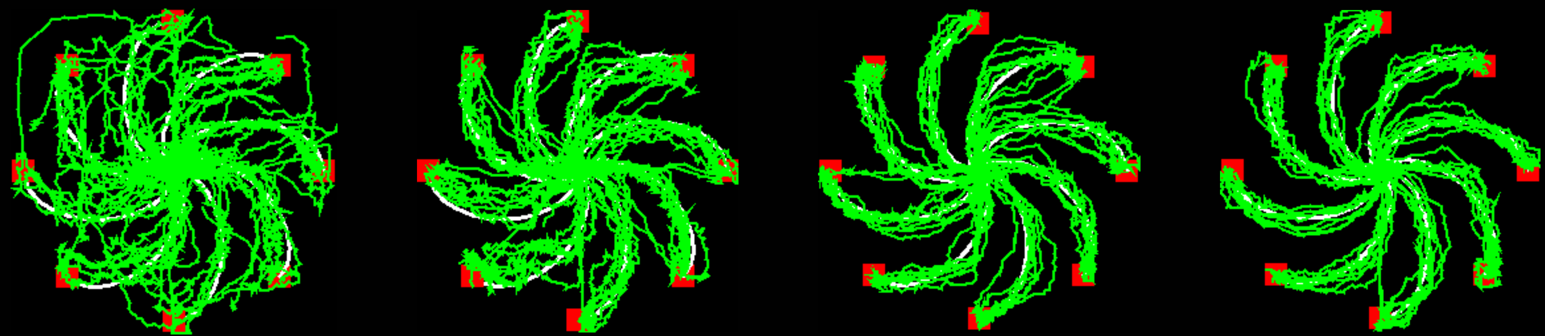
Visuomotor adaptation ASM Condition 'Indirect mode'

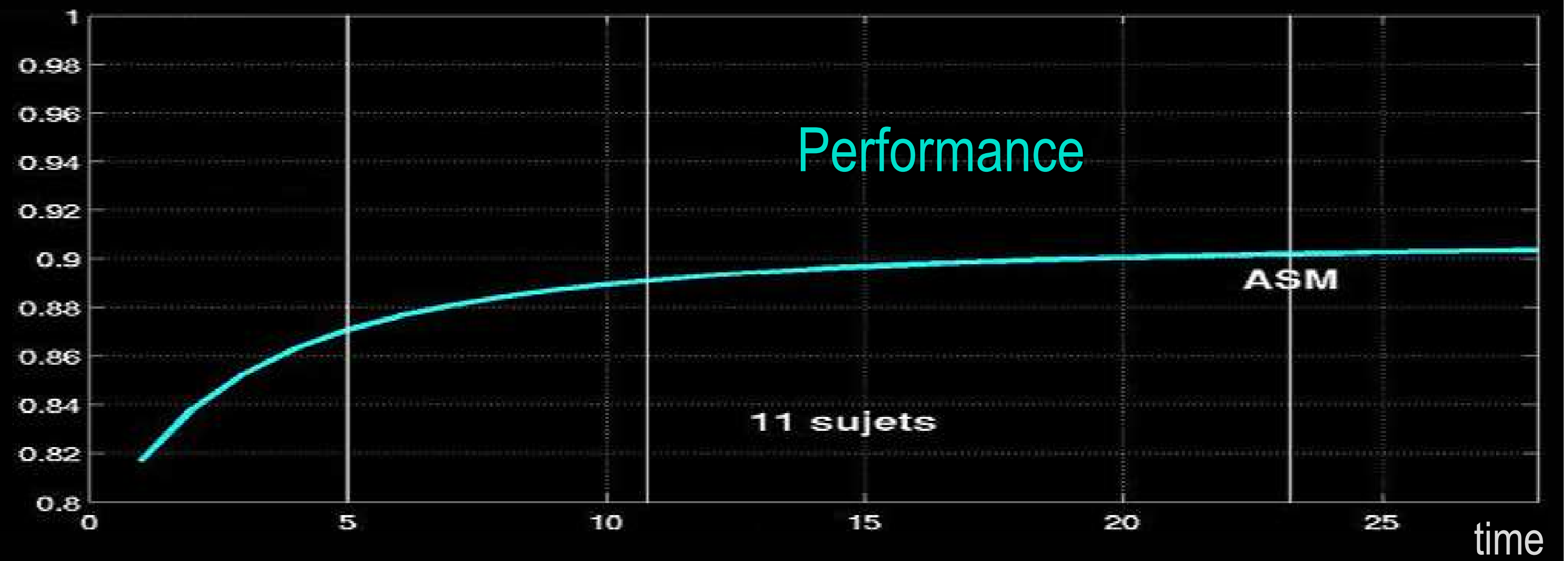




Functional network : performance

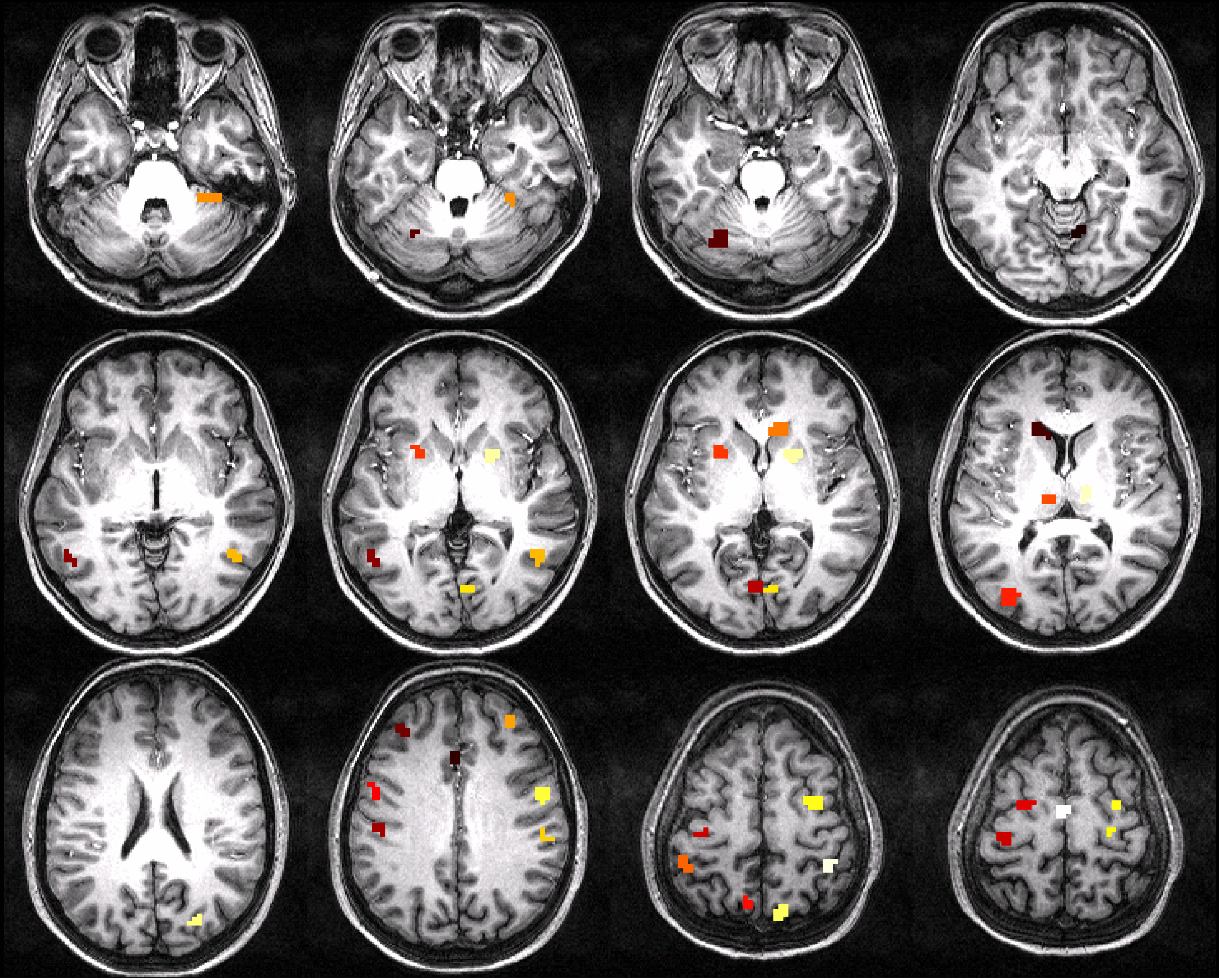
Does performance improvement reflect changes in functional connectivity?





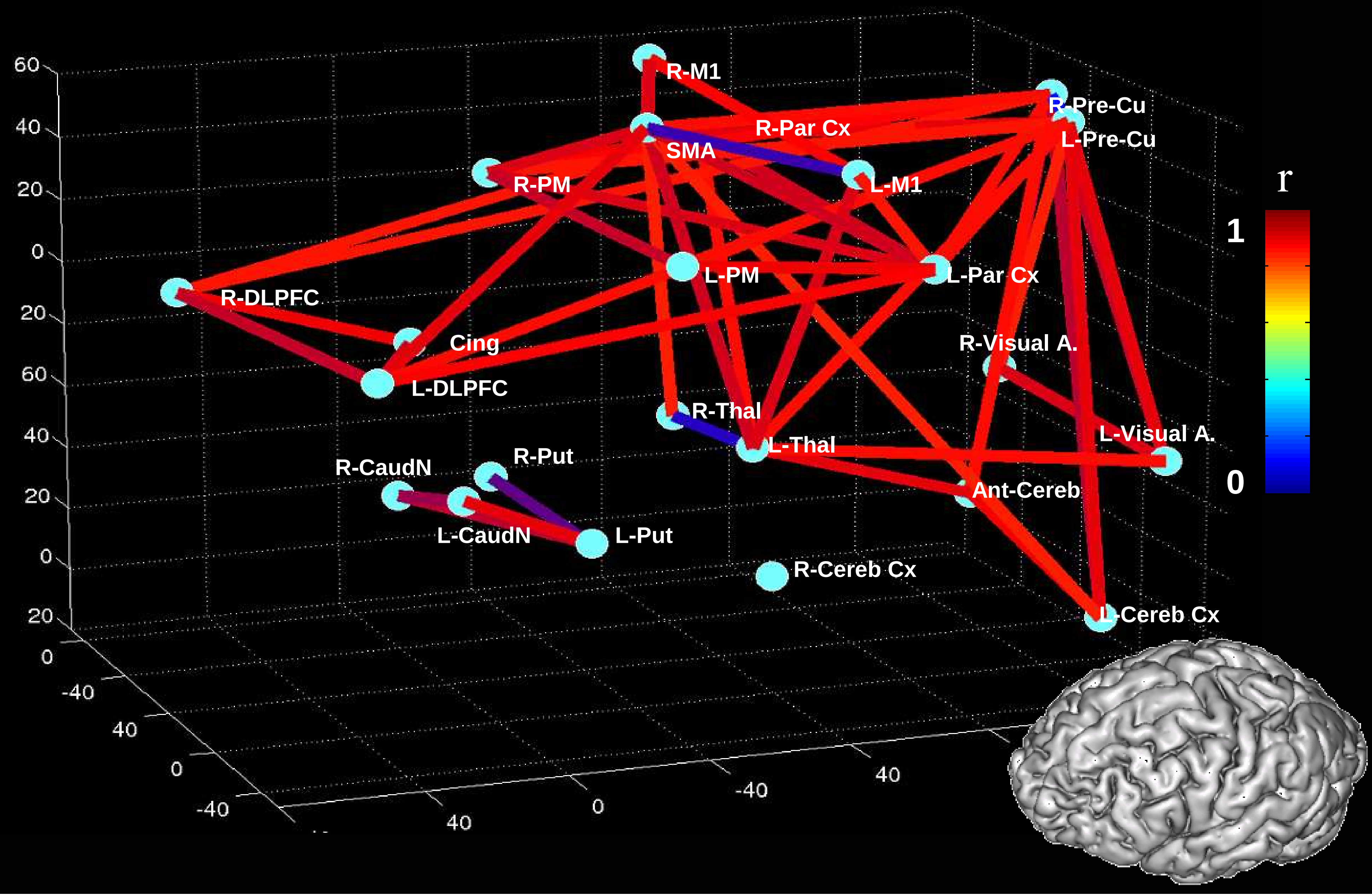
Functional network : activation network

Brain units
(15 voxels)



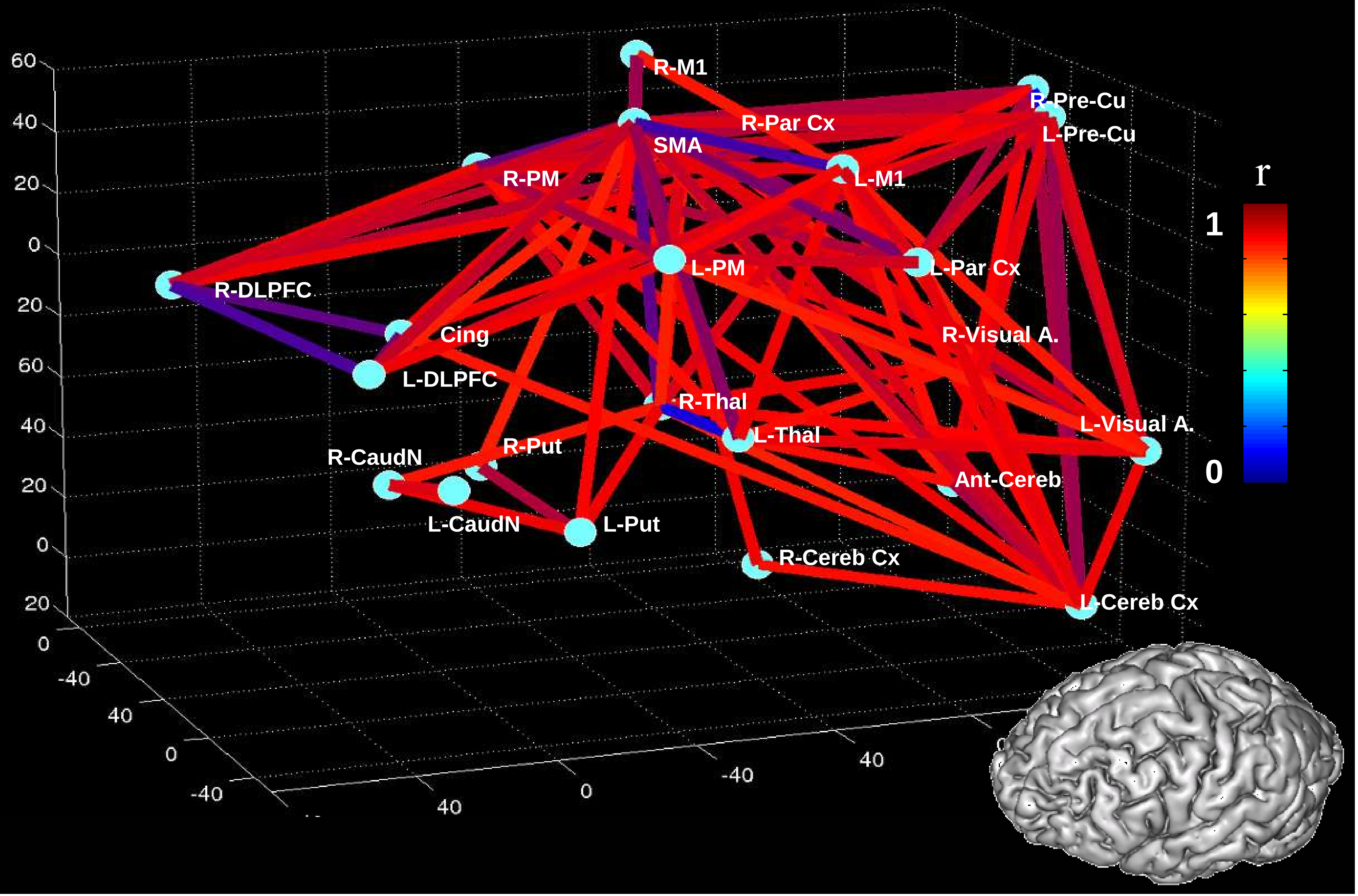
Functional network

Block 1 (*p<0.01*)



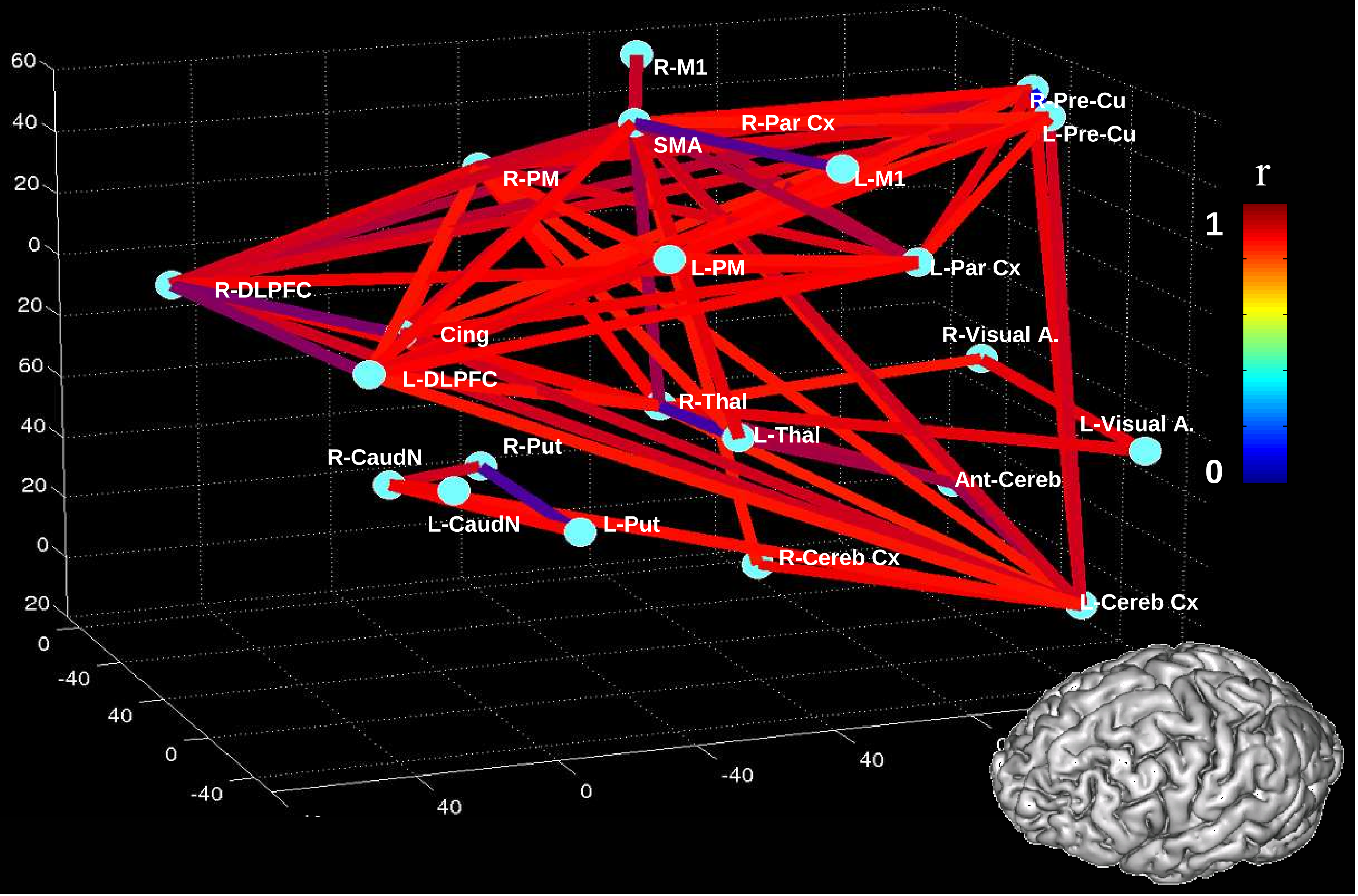
Functional network

Block 2 (*p*<0.01)



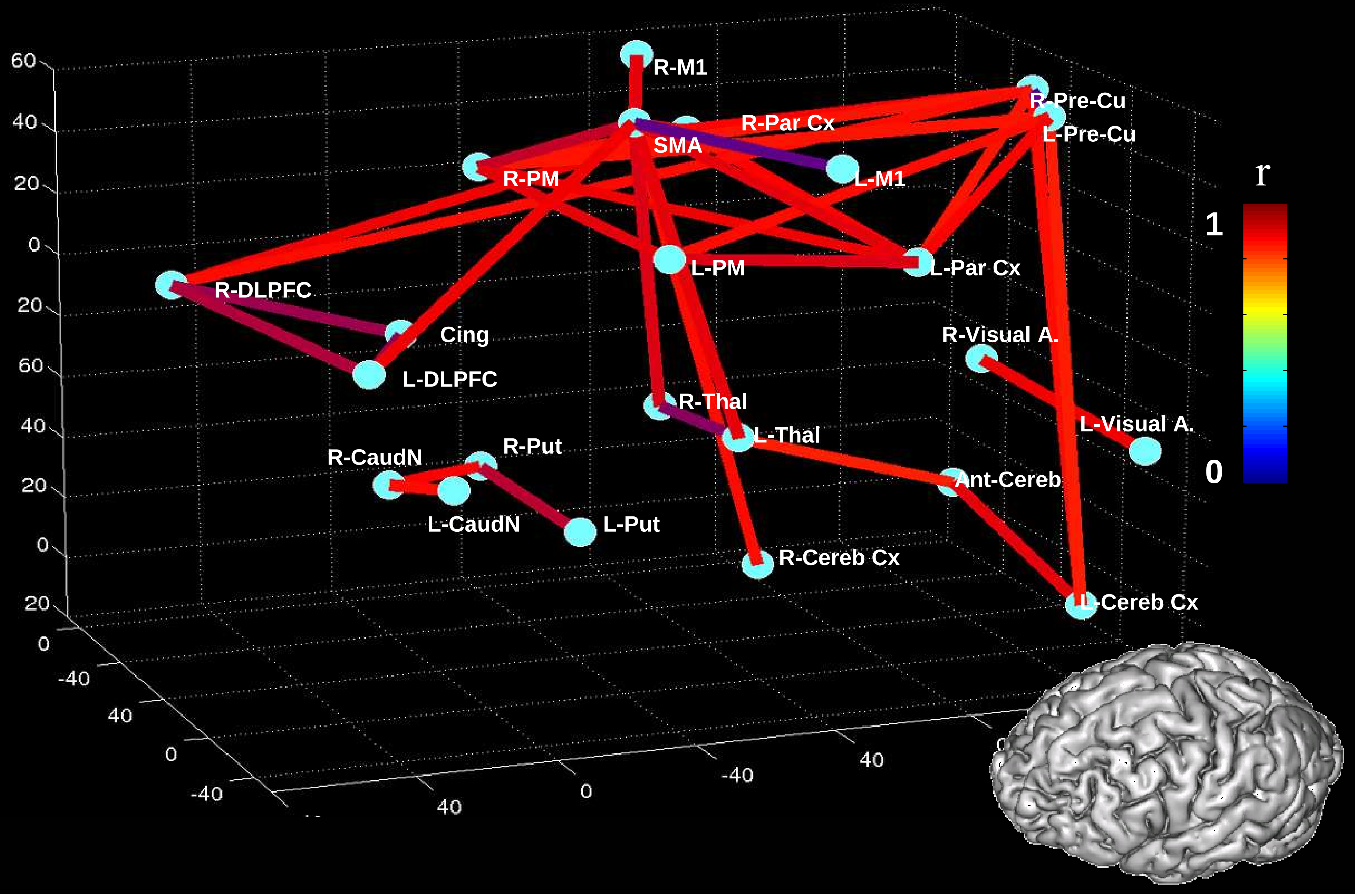
Functional network

Block 3 (*p<0.01*)

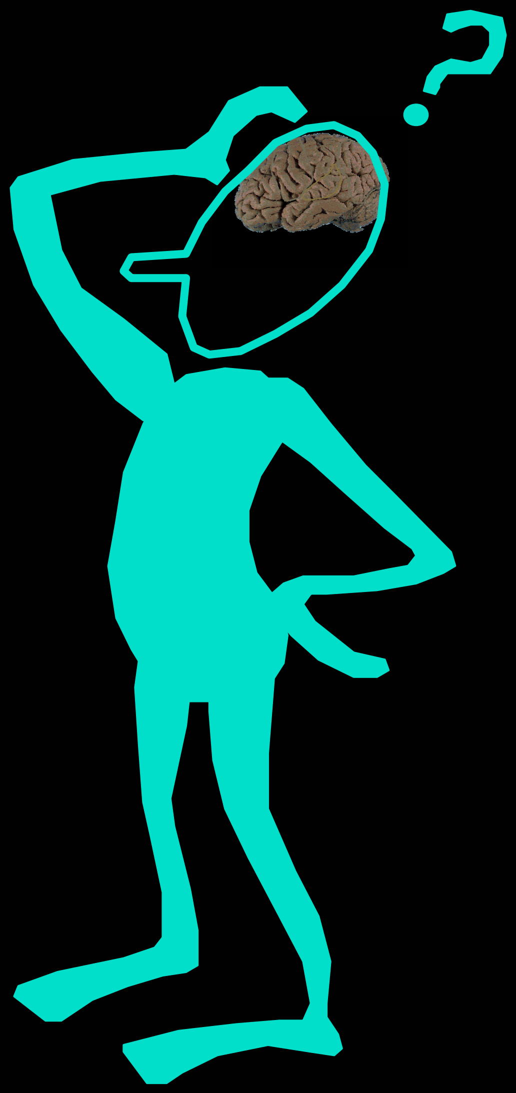


Functional network

Block 4 ($p<0.01$)



Dynamical functional connectivity

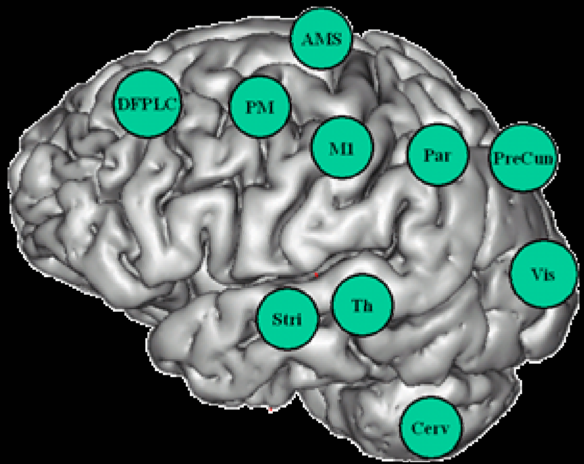


'The graphs are complex'

Global interaction effect: increasing then decreasing number of interactions

Dynamical functional connectivity: Testing for global interaction over time

$$\mathbf{n}_t = \text{Number } \{(i,j);\ \rho_{ij} > 0.333\} \text{ at } t$$



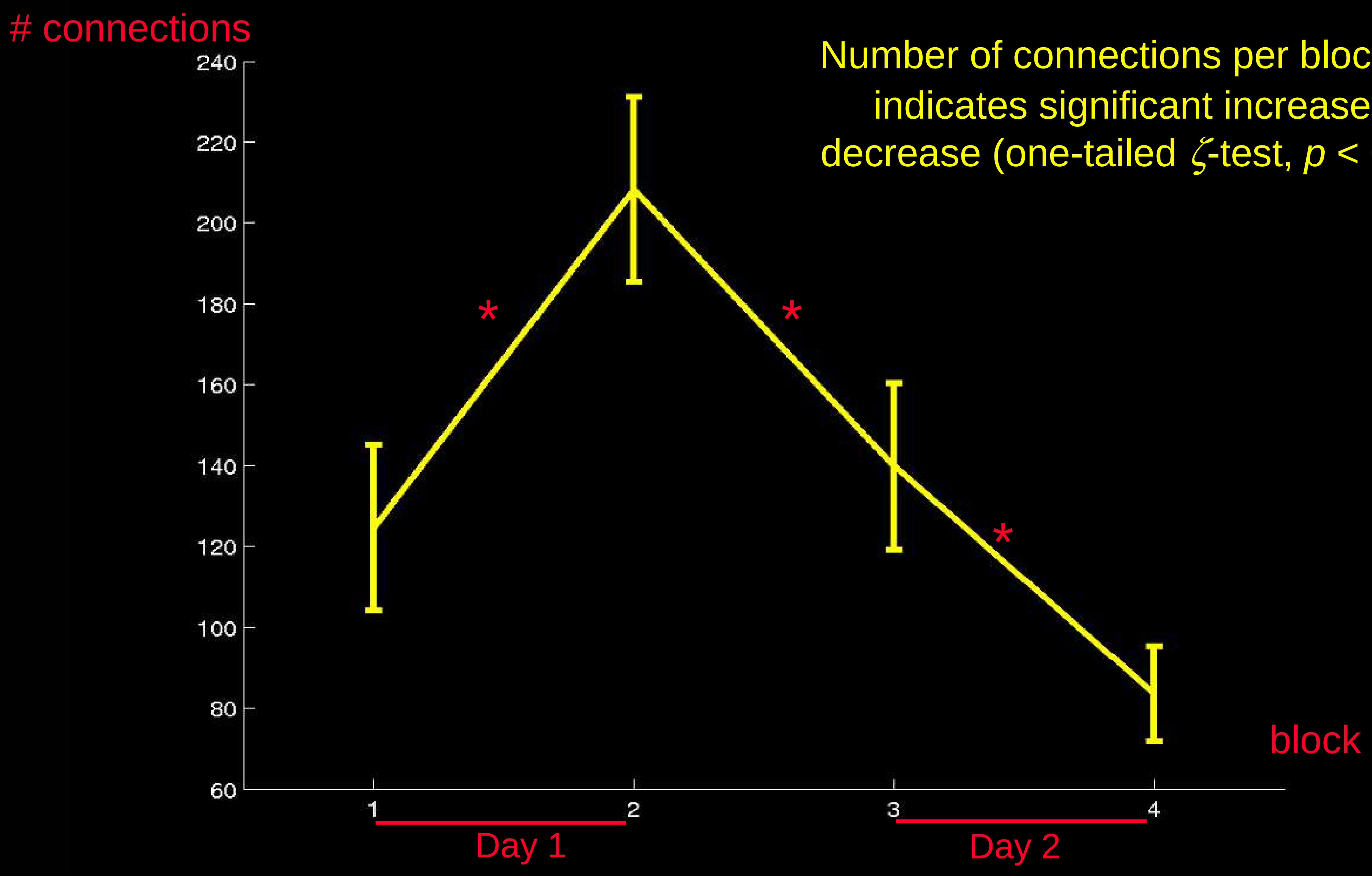
Data ~ N(μ, Σ)

Covariance Σ ~ Inv-Wishart(ν, **S**)

Resampling method

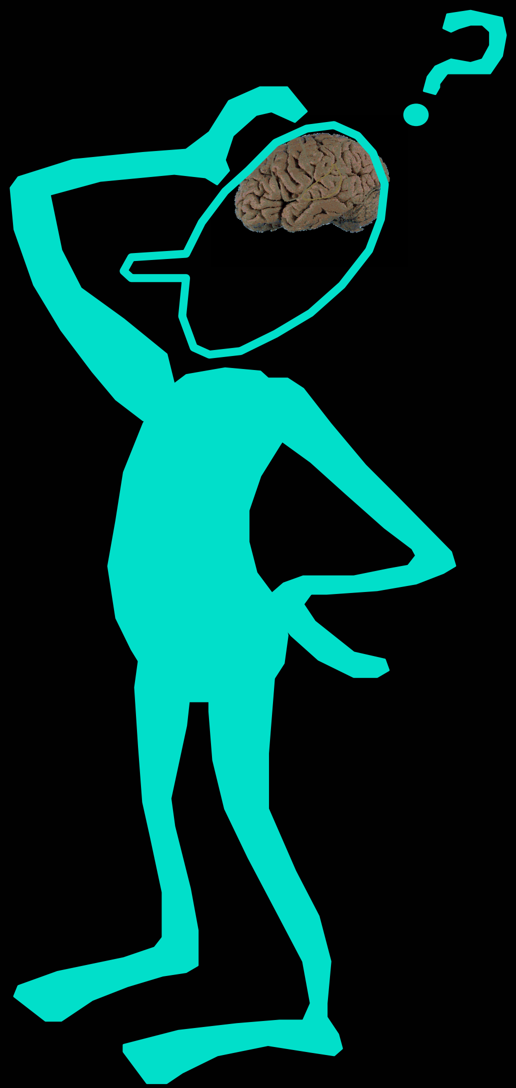
1. Simulate B (~1000) random variable Σ_t using the Inv-Wishart distribution and construct a correlation matrix ρ_t. Construct a random variable n_t
2. The empirical distribution function $n_{1t}\ n_{2t}\ \ldots\ n_{Bt}$ approximates the distribution of n_t for large B.

Dynamical functional connectivity: Testing for global interaction over time



Number of connections per block. A * indicates significant increase or decrease (one-tailed ζ-test, $p < 0.05$).

Dynamical functional connectivity



Quantifying changes of interaction between areas and relating it to the cognitive model of motor adaptation

Dynamical functional connectivity: Testing for dynamics

$$H0 : \rho_{ij}(t) \neq 0 \text{ and } \rho_{ij}(t') \neq 0 \text{ and } \rho_{ij}(t) = \rho_{ij}(t')$$

Statistical test

$$\zeta_{ij}(t,t') = \frac{\rho_{ij}(t) - \rho_{ij}(t')}{\sqrt{\nu(t) + \nu(t')}}$$

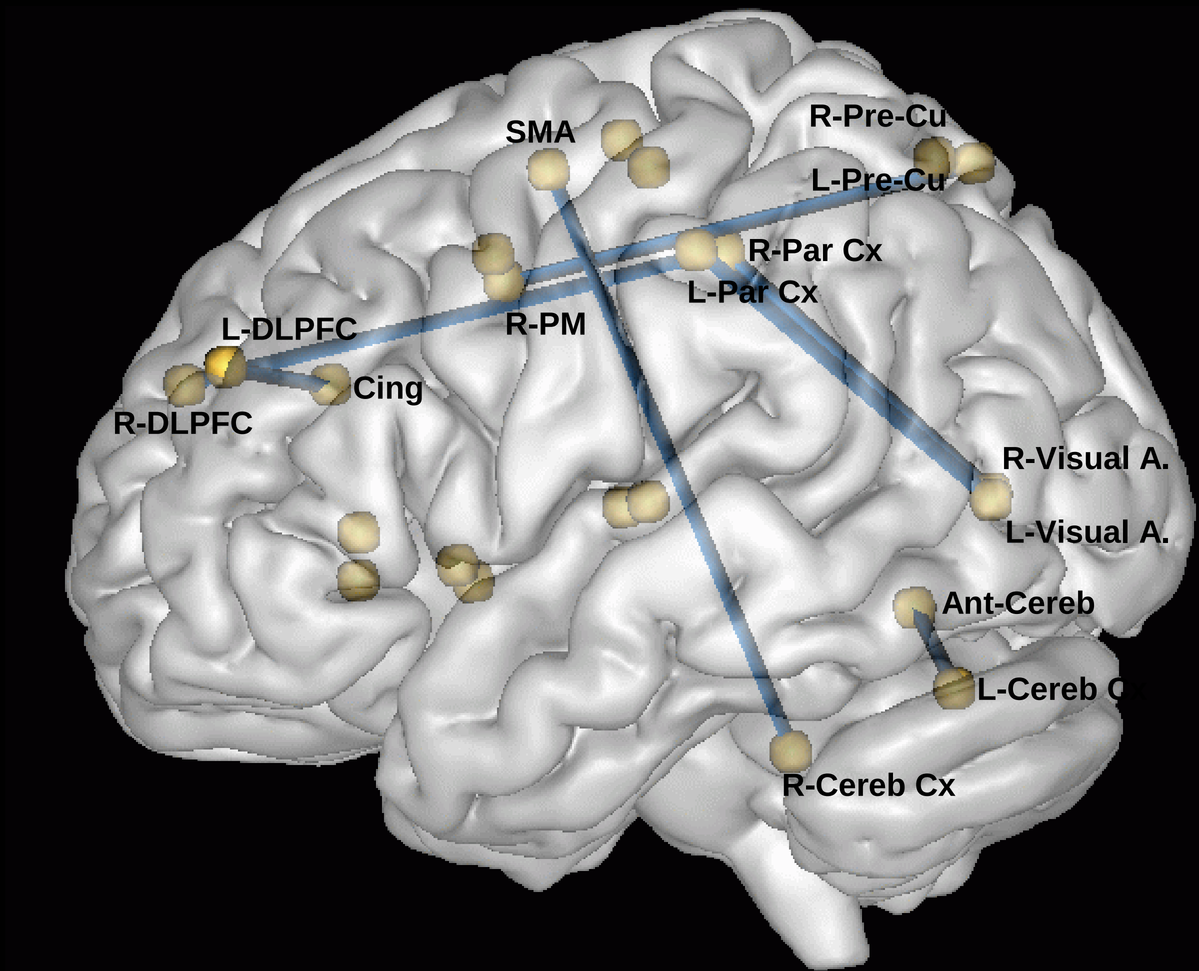
Resampling method

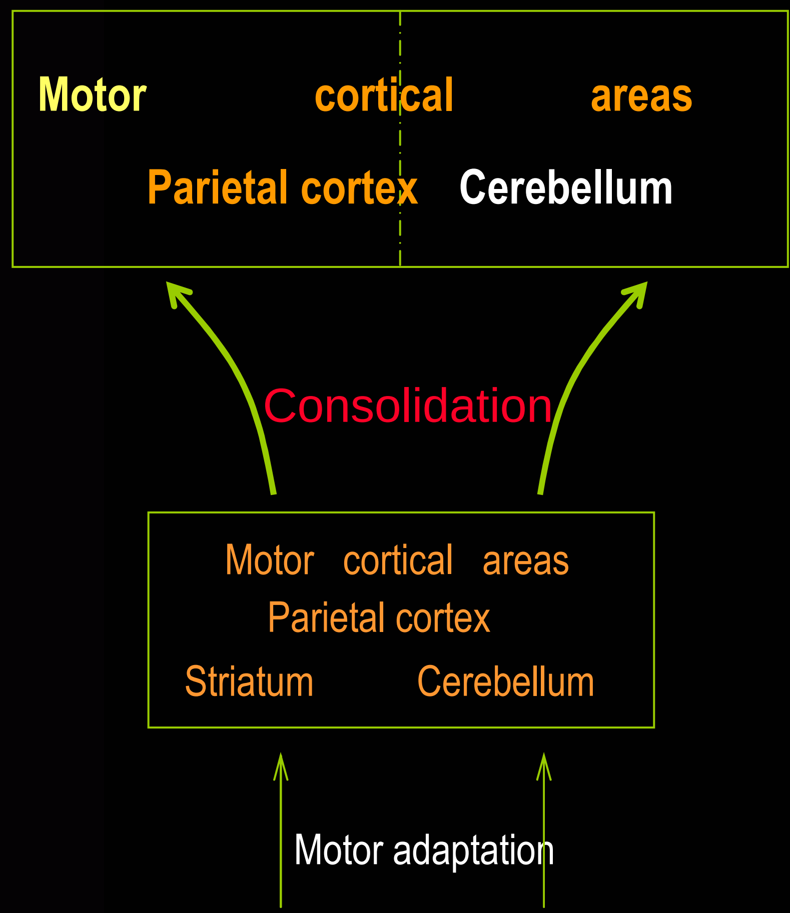
1. Simulate B (~1000) random variable S_t, $t=1,T$ using the Inv-Wishart distribution and construct a correlation matrix ρ_t, $t=1,T$. Construct a random variable $\zeta_{ij}(t,t')$

2. The empirical distribution function $\zeta^1_{ij}(t,t')$, $\zeta^2_{ij}(t,t')$ … $\zeta^B_{ij}(t,t')$ approximates the distribution of $\zeta_{ij}(t,t')$ for large B.

Dynamical functional connectivity: Testing for dynamics

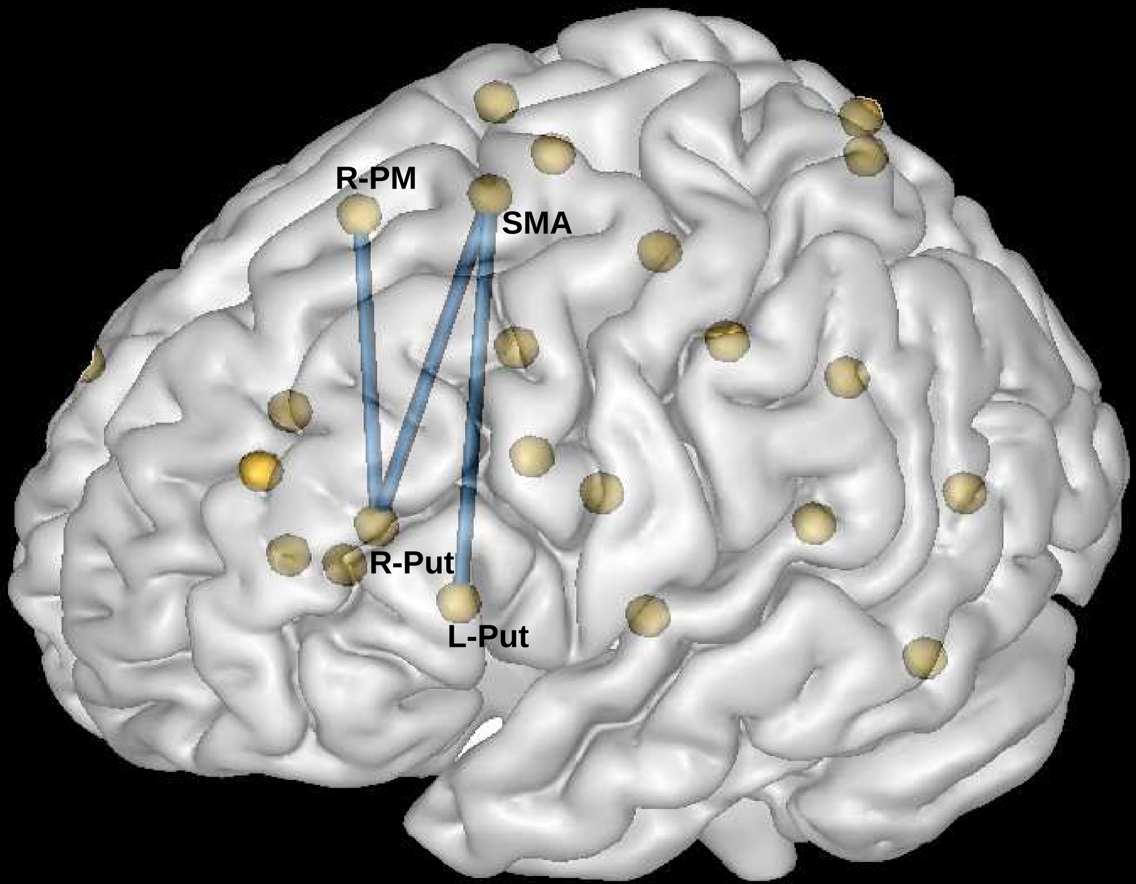
Specialization graph: connections significantly increased from block 1 to 2, not significantly decreased from block 2 to 4, and still significant in block 4 (one-tailed ζ-test, p<*0.05*)

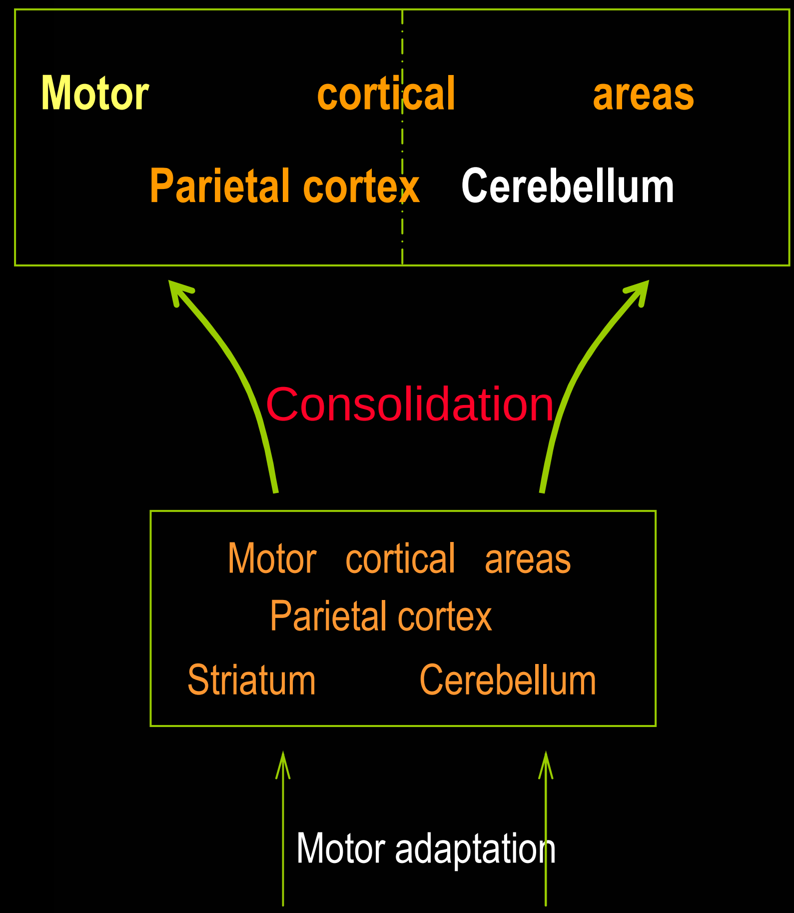




Dynamical functional connectivity: Testing for dynamics

Specialization graph: connections significantly increased from block 1 to 2, significantly decreased from block 2 to 4, and not significant in block 4 (one-tailed ζ-test, $p<0.05$)



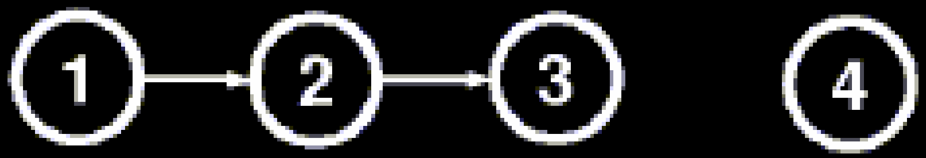


Functional connectivity : direct or indirect interaction

Does interactivity reflect direct changes in functional connectivity ?

Functional connectivity : Conditional interactivity

Gap between effective and correlational connectivity



Model

$$\begin{aligned} Y_1 &= & & & E_1 \\ Y_2 &= \lambda \cdot Y_1 & & + & E_2 \\ Y_3 &= & \mu \cdot Y_2 & + & E_3 \\ Y_4 &= & & & E_4 \end{aligned}$$

Effective connectivity

$$\begin{aligned} \mathrm{Corr}[Y_1, Y_4] &= 0 \\ \mathrm{Corr}[Y_1, Y_2] &= \frac{\lambda}{\sqrt{\lambda^2 + 1}} \neq 0 \\ \mathrm{Corr}[Y_1, Y_3] &= \frac{\lambda\mu}{\sqrt{\lambda^2\mu + \mu}} \neq 0 \end{aligned}$$

Conditional correlation

$$\begin{aligned} \mathrm{Corr}[Y_1, Y_2 | Y_3] &= \frac{\lambda}{\sqrt{(\lambda^2 + 1)(\mu^2 + 1)}} \neq 0 \\ \mathrm{Corr}[Y_1, Y_3 | Y_2] &= 0 \end{aligned}$$

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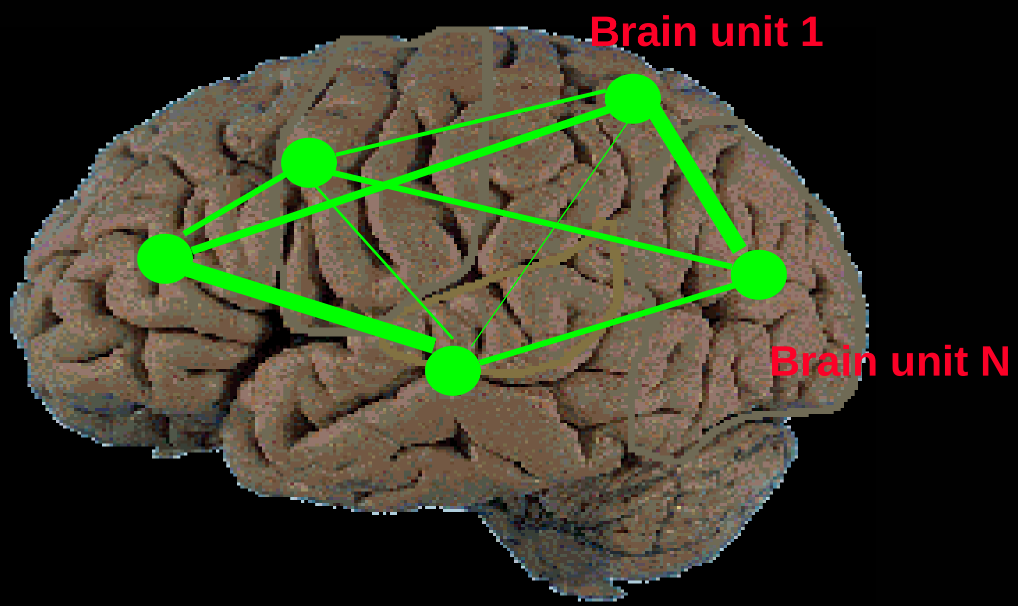
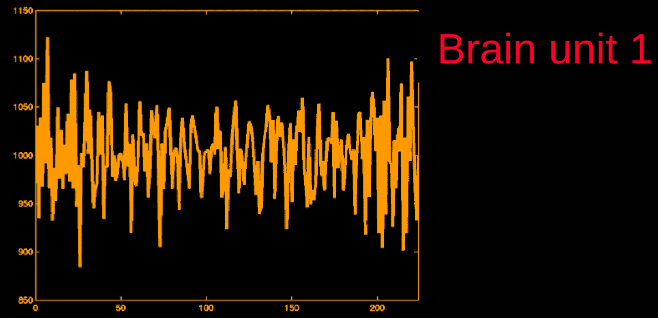
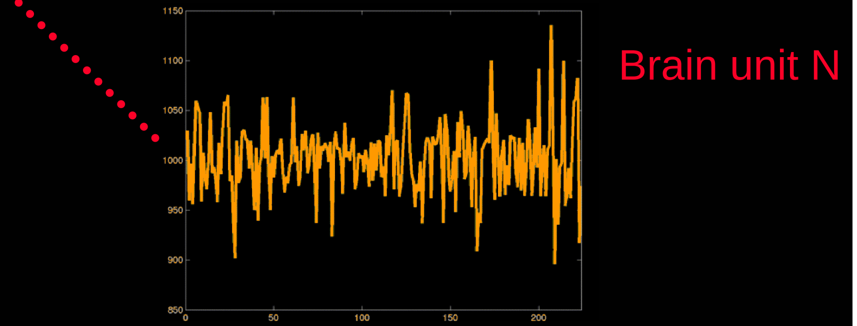
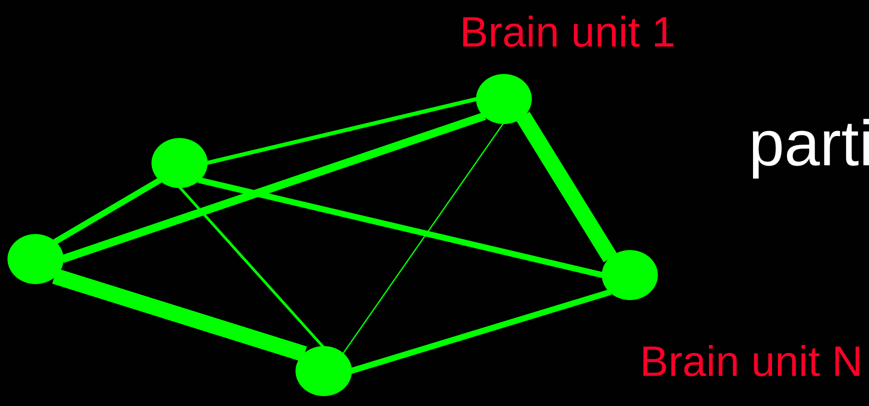
Functional connectivity : Conditional interactivity









partiel correlation $\pi_{ij} \in [-1,1]$

$\pi_{ij} = 0$: no direct interaction

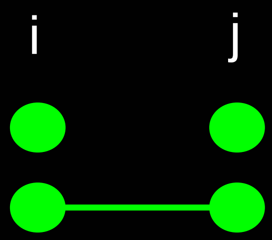
$\pi_{ij} \neq 0$: not independent

Functional connectivity : Conditional independence graph model

$p(\gamma \mid H, \mathbf{y}) \propto p(\mathbf{y} \mid H, \gamma) \cdot p(\gamma \mid H)$

(Bayesian approach)

graph model (qualitative)



$\gamma_{ij} = 0 \Rightarrow \pi_{ij} = 0$

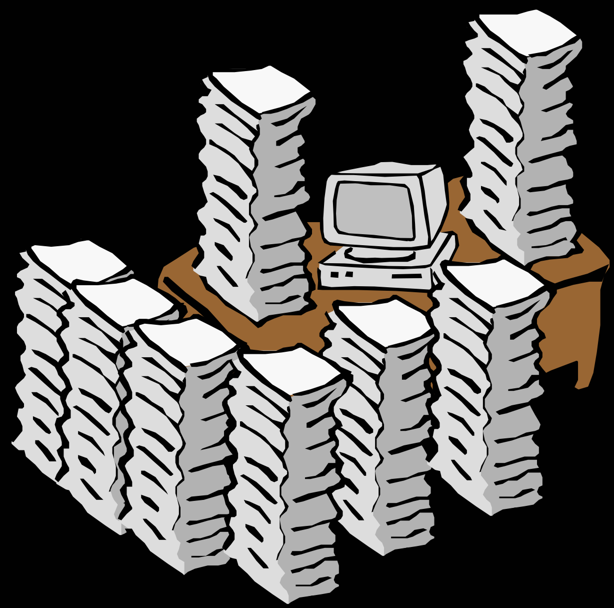
$\gamma_{ij} = 1 \Rightarrow \pi_{ij} \in [-1,1]$

data model (quantitative)

$\mathbf{y}_t \mid H, \pi \sim N(\mathbf{m}, \mathbf{V})$

- $\mathbf{V}$ → variance
- $\mathbf{m}$ → mean

a priori



Marrelec G et al. IEEE ISBI, 2002

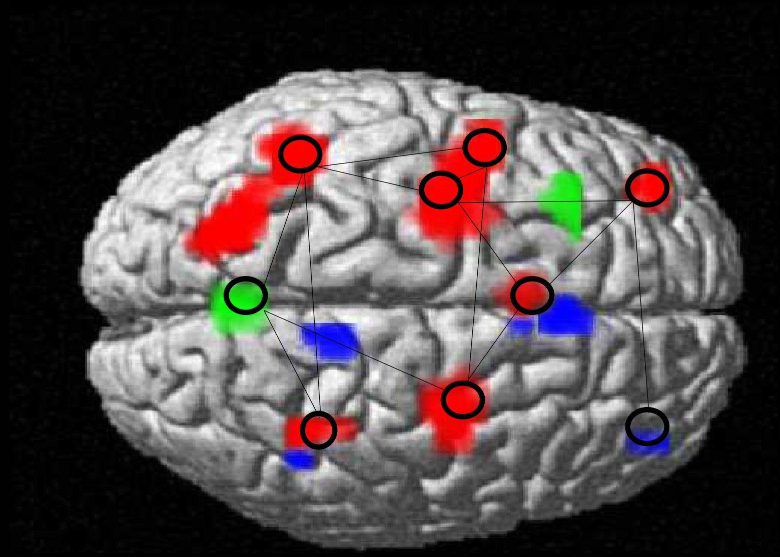
Functional connectivity : Conditional independence graph model

$$p(\gamma \mid H,\mathbf{y}) \propto p(\gamma \mid H)\, 2^{-l(\gamma)}\, N(\mathbf{m}_0,\mathbf{V}_{00}\,;\, 0_0)$$

$\gamma^{(0)}$ → sampling of $\gamma^{(0)}_{ij}$ according to $p(\gamma_{ij} \mid H,\mathbf{y})$

$\gamma^{(n-1)}$ ↓ $\gamma^{(n)}$ → sampling according to $p(\gamma_{ij} \mid H,\mathbf{y},\gamma_{kl\neq ij})$ $\propto p(\gamma_{ij},\gamma_{kl\neq ij} \mid H,\mathbf{y})$

$$\begin{pmatrix} \gamma^{(n)}_{12} \\ \gamma^{(n)}_{13} \\ \dots \\ \gamma^{(n)}_{N-1,N} \end{pmatrix} \rightarrow \begin{pmatrix} \gamma^{(n+1)}_{12} \\ \gamma^{(n)}_{13} \\ \dots \\ \gamma^{(n)}_{N-1,N} \end{pmatrix} \rightarrow \dots\dots \rightarrow \begin{pmatrix} \gamma^{(n+1)}_{12} \\ \gamma^{(n+1)}_{13} \\ \dots \\ \gamma^{(n+1)}_{N-1,N} \end{pmatrix}$$

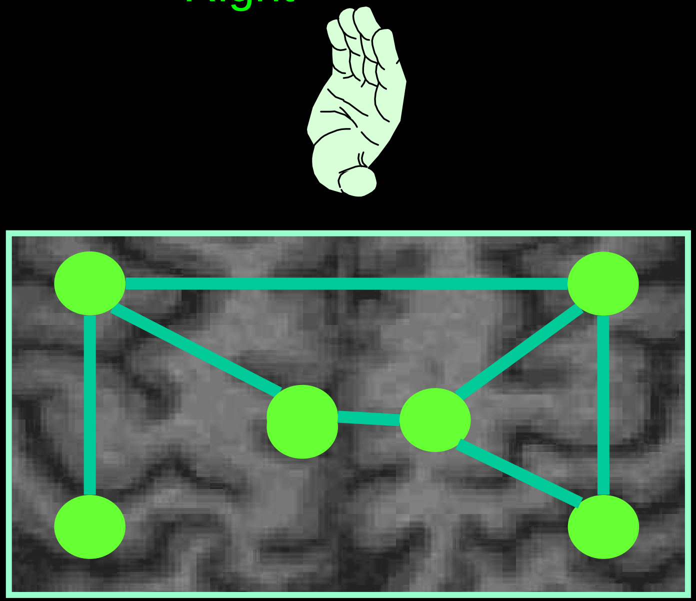


graph estimation: $\gamma_e = \mathrm{MAP}[p(\gamma \mid H,\mathbf{y})]$; $\gamma_m = E[\gamma \mid H,\mathbf{y}]$

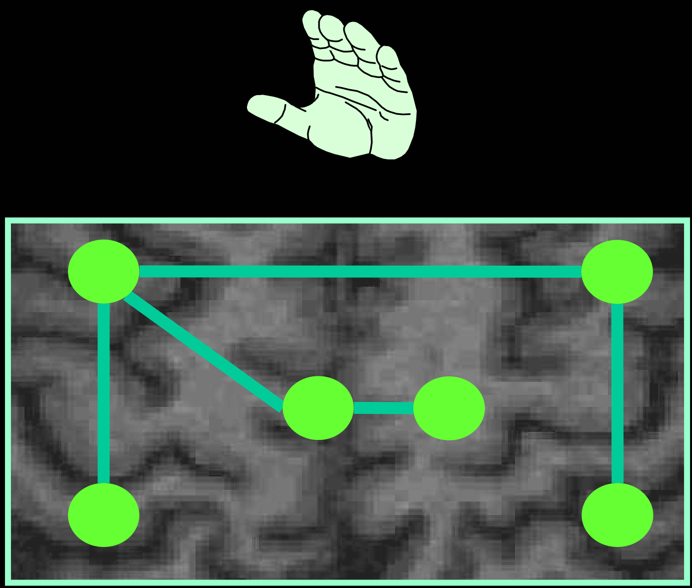
Functional connectivity : Conditional independence graph model

Simple motor task using fMRI

Right



Left



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