Can E-I balance provide a mechanism for Brain network recovery to normalcy

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Outline

Alteration of connectivity and BOLD dynamics following lesion

Impact of virtual brain lesions and altered structural Connectivity: Impact on resting-State FC

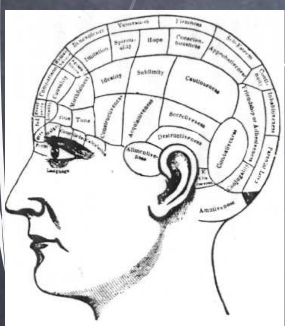
Functional Connectivity recovery to normalcy: reorganization of neurocognitive networks using robust inhibitory plasticity mechanism

Outlook

Division in processing: Localization versus globalism

Localism

- Functions are localised in anatomic cortical regions
- Damage to a region results in loss of function

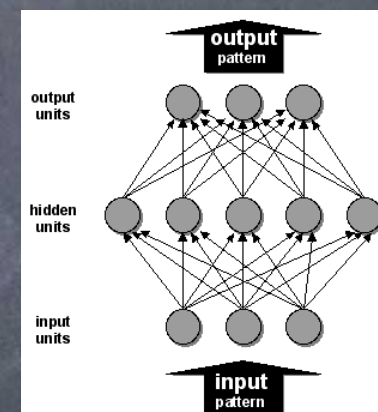


Functional Segregation

- Functions are carried out by specific areas/cells in the cortex that can be anatomically separated

Globalism

- The brain works as a whole, extent of brain damage is more important than its location



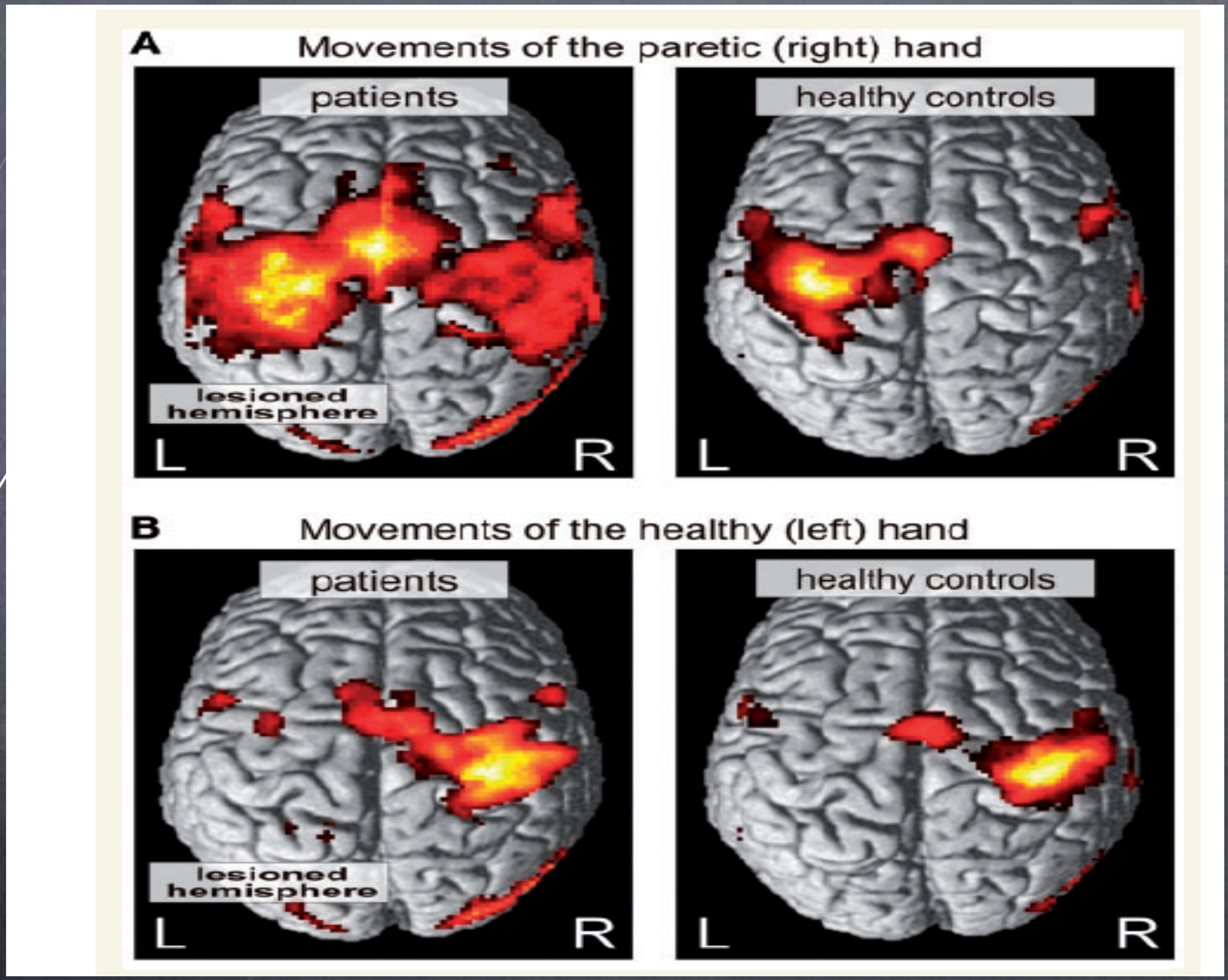
Connectionism

- Networks of simple connected units

Functional Segregation
Different areas of the brain are specialised for different functions

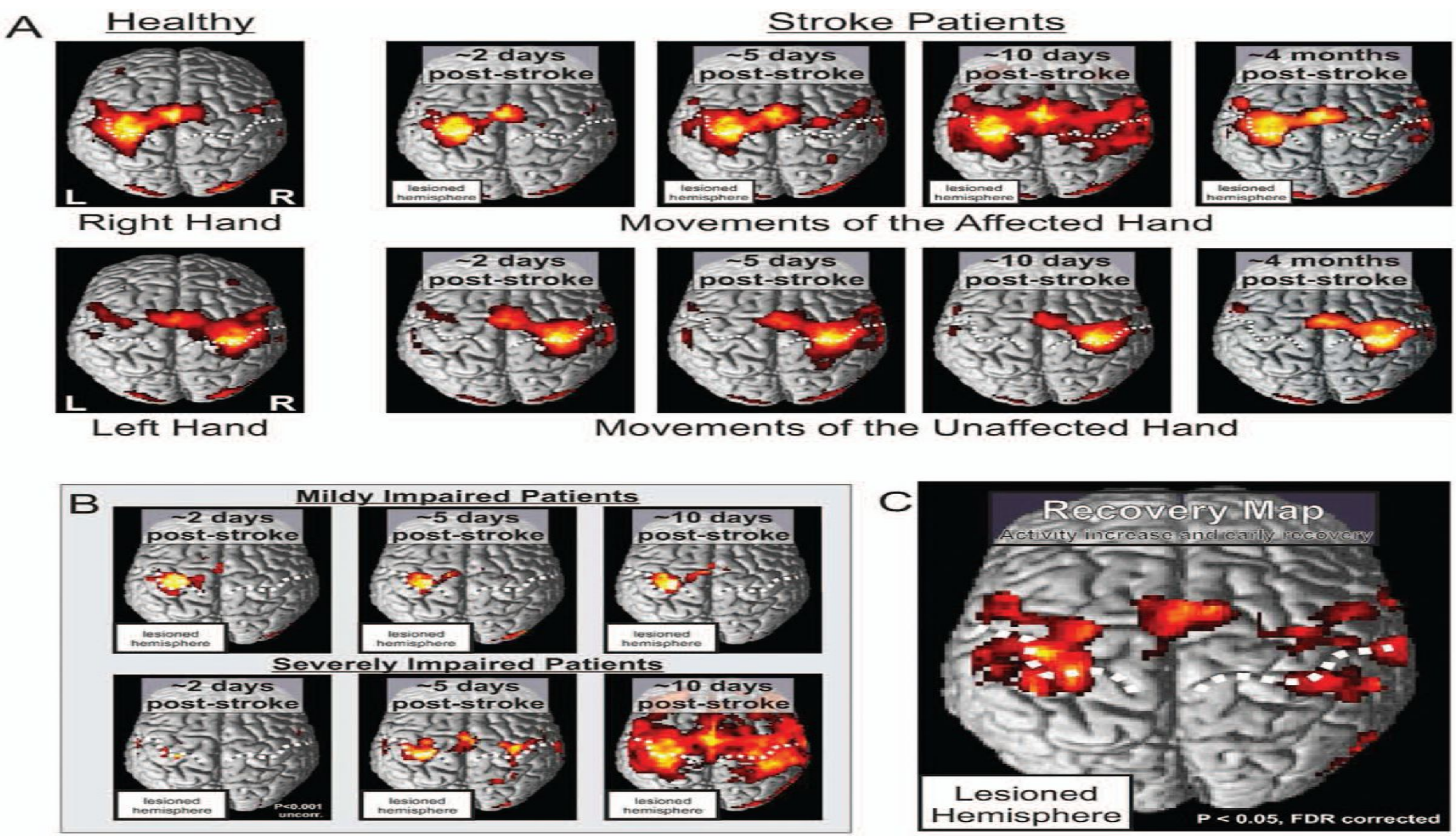
Functional Integration
Networks of interactions among specialised areas

Movement generations and hemodynamic response on the contralesional side of Ischemic stroke patients patients



Grefeks et al.(2011) Brain

Tracking Longitudinal progression in motor network activity in stroke patients



Christian Grefkes, and Nick S. Ward
Neuroscientist 2013;20:56-70

Outline

Introduction to Brain Networks and topological connectivity measures

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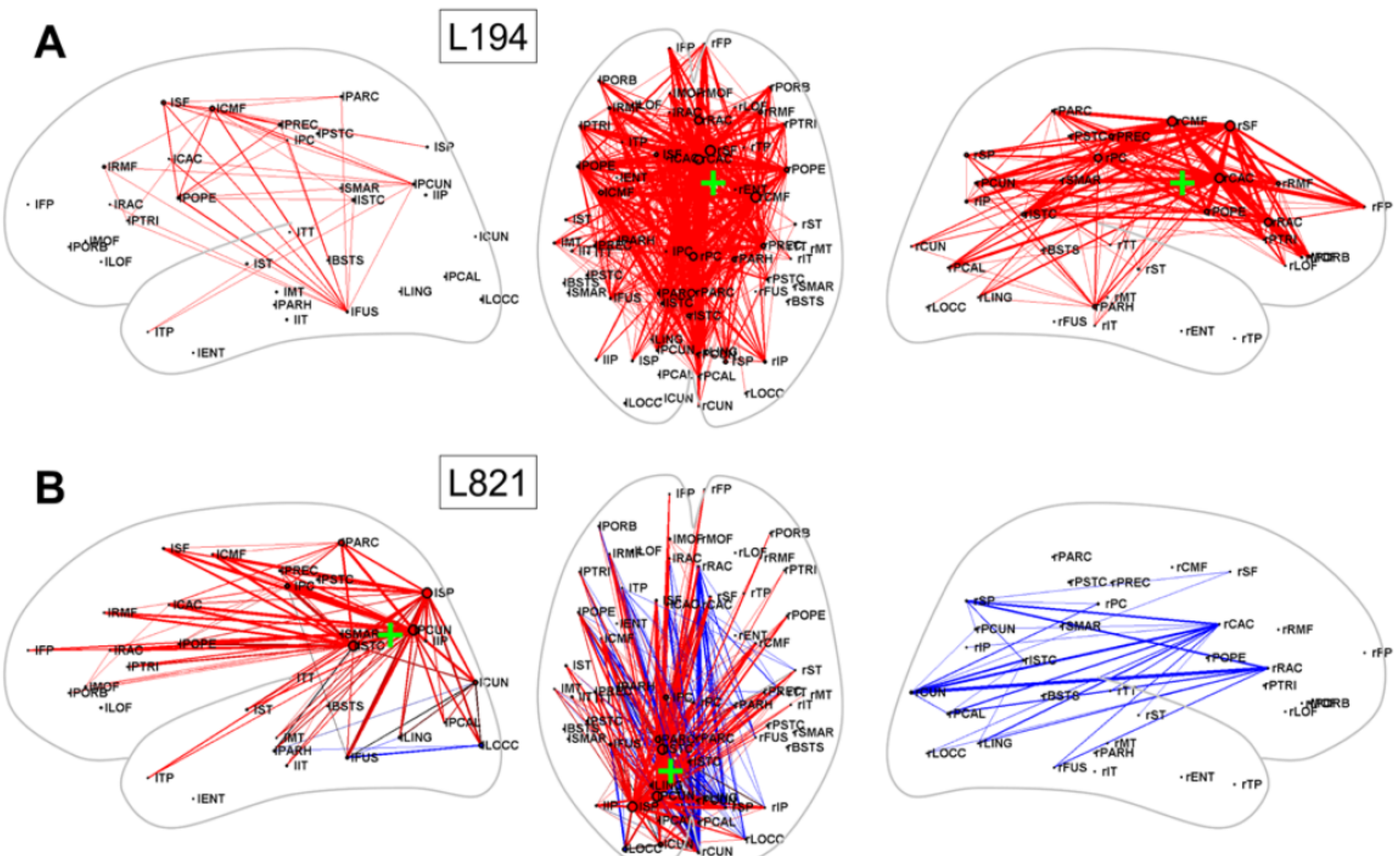
Table of *in-silico* lesion areas covering 80%-90% of the cerebral cortex

	Right Hemisphere				
	Lesion name	**ROI center**	**Talairach coordinate**	**Center region**	**Lesioned regions**
Cortical midline	L323	323	(6, −56, 38)	rPCUN	rCUN, rISTC, rPCUN
	L194	194	(5 16 31)	rCAC	rCAC, rCMF, rSF
Parietal and temporal cortex	L308	308	(47 −51 22)	rIP	rBSTS, rIP, rSMAR
	L247	247	(62 −31 28)	rSMAR	rPSTC, rSMAR, rTT
	L472	472	(65 −32 10)	rST	rBSTS, rMT, rST, rSMAR, rTT
	L439	439	(50 −11 −29)	rIT	rENT, rIT, rST, rTP
Frontal cortex	L86	86	(7 48 21)	rSF	rCAC, rFP, rRAC, rRMF, rSF
	L138	138	(39 9 51)	rCMF	rCMF, rPREC
	L57	57	(40 9 21)	rPOPE	rCMF, rPOPE
Sensory, motor	L360	360	(26 −94 −6)	rLOCC	rLOCC, rLING, rPCAL
	L162	162	(34 −23 46)	rPREC	rPSTC
	Left Hemisphere				
	Lesion name	**ROI center**	**Talairach coordinate**	**Center region**	**Lesioned regions**
Cortical midline	L821	821	(−8 −57 47)	lPCUN	lISTC, lPCUN, lSP
	L692	692	(−7 26 26)	lCAC	lCAC, lRAC, lSF
Parietal and temporal cortex	L810	810	(−45 −50 20)	lIP	lBSTS, lIP
	L746	746	(−58 −25 28)	lSMAR	lPSTC, lSMAR
	L971	971	(−61 −36 12)	lST	lBSTS, lMT, lSMAR, lTT
	L938	938	(−44 −10 −26)	lIT	lENT, lIT, lMT, lPARH, lST, lTP
Frontal cortex	L584	584	(−8 52 17)	lSF	lCAC, lFP, lRAC, lRMF
	L636	636	(−39 7 42)	lCMF	lCMF, lPREC
	L555	555	(−42 22 18)	lPOPE	lCMF, lPOPE, lPTRI, lRMF
Sensory, motor	L856	856	(−25 −93 −7)	lLOCC	lLOCC, lLING, lPCAL
	L661	661	(−34 −9 52)	lPREC	lPREC

Vattikonda et al. (2016) Neuroimage

Lesion severity in the cortical midline Hub area DMN



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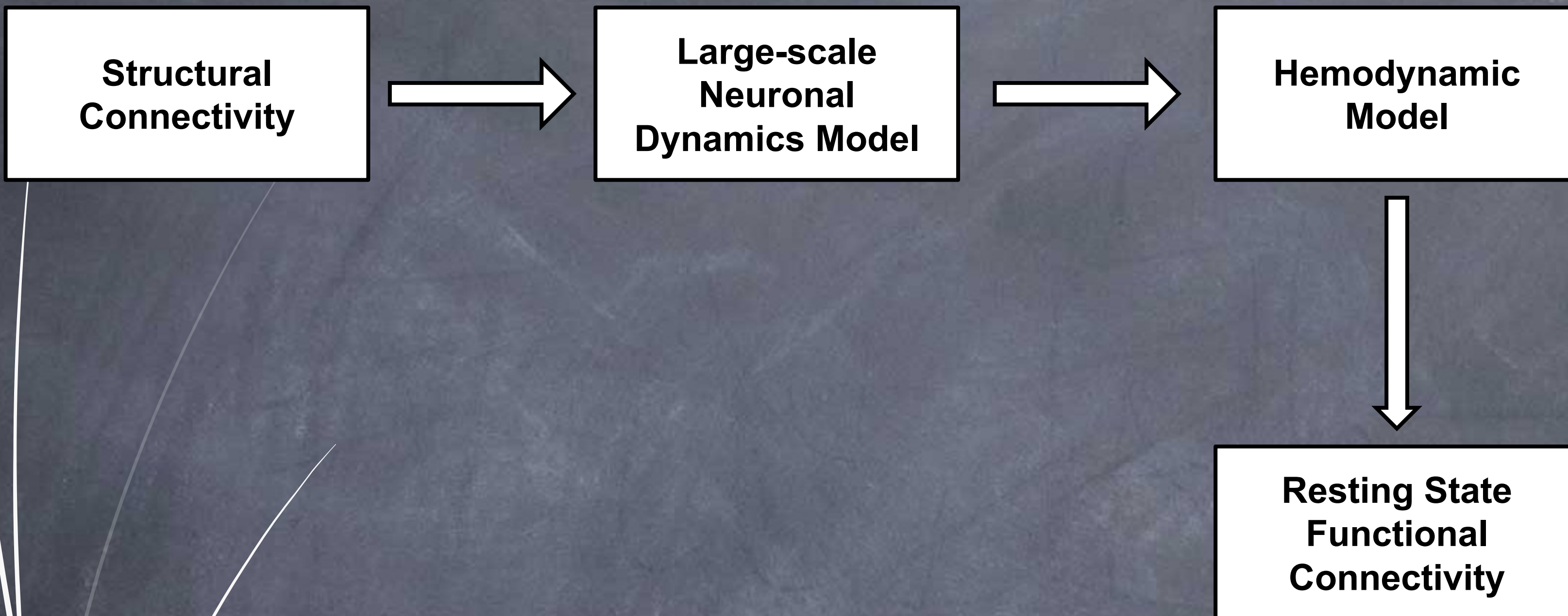
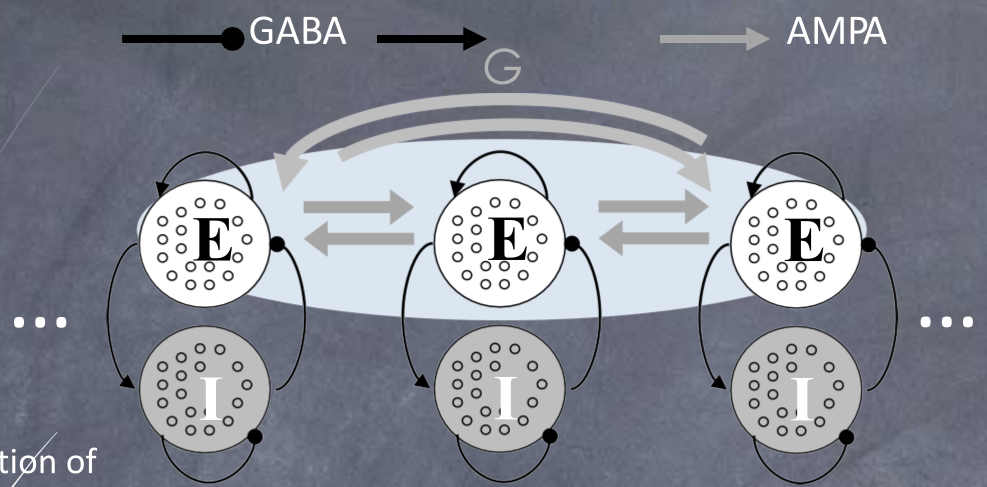
Predicting rs-FC from SC

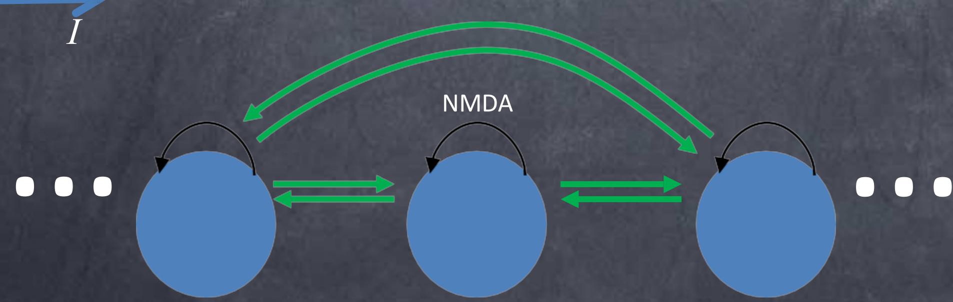


Structural Connectivity : Obtained from DTI
Neuronal Dynamics Model : Dynamic Mean Field model
Hemodynamic Model : Balloon-Windkessel hemodynamic model
rs-FC : Pairwise Correlation matrix of BOLD time series

Mean field approximation



Mean field approx.



$$\tau_{NMDA} \gg \tau_{AMPA}, \tau_{GABA}$$

linear approximation of the transfer function of the inhibitory cells
(inhibitory cells typically fire between 8 –15 Hz. Within this range, the F-I curve is almost linear)

Neurons

Population synaptic activity

Reduced dynamic mean field model

Wong and Wang (2006)

Model Contd...

$$I_i^{(E)} = W_E I_0 + w_+ J_{NMDA} S_i^{(E)} + G J_{NMDA} \Sigma_j C_{ij} S_j^{(E)} - J_i S_i^{(I)} \quad (1)$$

$$I_i^{(I)} = W_I I_0 + J_{NMDA} S_i^{(E)} - S_i^{(I)} \quad (2)$$

$$r_i^{(E)} = \frac{a_E I_i^{(E)} - b_E}{1 - exp(-d_E(a_E I_i^{(E)} - b_E))} \quad (3)$$

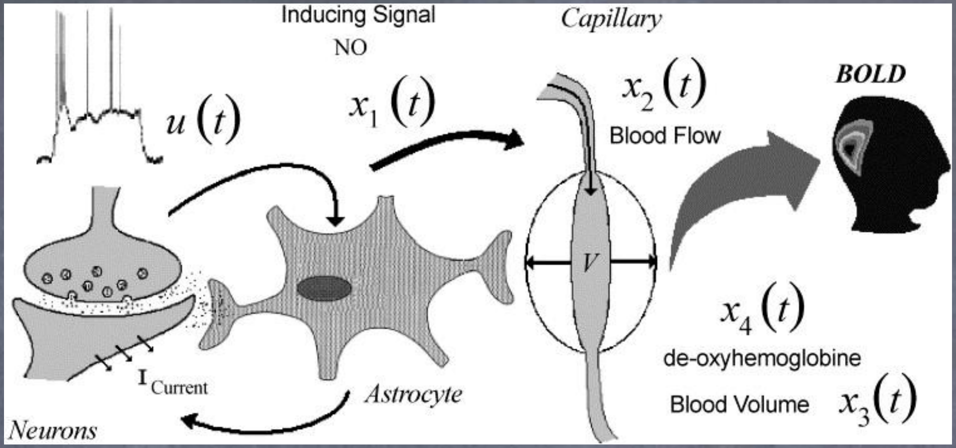
$$r_i^{(I)} = \frac{a_I I_i^{(I)} - b_I}{1 - exp(-d_I(a_I I_i^{(I)} - b_I))} \quad (4)$$

$$\frac{dS_i^{(E)}(t)}{dt} = -\frac{S_i^{(E)}}{\tau_E} + (1 - S_i^{(E)})\gamma r_i^{(E)} + \sigma v_i(t) \quad (5)$$

$$\frac{dS_i^{(I)}(t)}{dt} = -\frac{S_i^{(I)}}{\tau_I} + r_i^{(I)} + \sigma v_i(t) \quad (6)$$

Deco et al. J.Neurosci (2014); Roy et al. (2015) Brain Connectivity

The Balloon-Windkessel model



Vessel ~ inflatable balloon

Riera et al. (2004)

$$\dot{x}_i = z_i - k_i x_i - \gamma_i \quad f_i - 1$$

$$\dot{f}_i = x_i$$

$$\tau_i \dot{v}_i = f_i - v_i^{1/\alpha}$$

$$\tau_i \dot{q}_i = \frac{f_i}{\rho}\left[1 - \quad 1 - \rho \quad ^{1/f_i}\right] - q_i v_i^{1/\alpha - 1}$$

$$BOLD_i = V_0\left[k_1(1 - q_i) + k_2(1 - q_i / v_i) + k_3 \quad 1 - v_i \quad\right]$$

For the *i*-th region, **synaptic activity z_i** causes an increase in a **vasodilatory signal x_i**. **Inflow f_i** responds to this signal with changes in blood **volume v_i** and **deoxyhemoglobin content q_i**

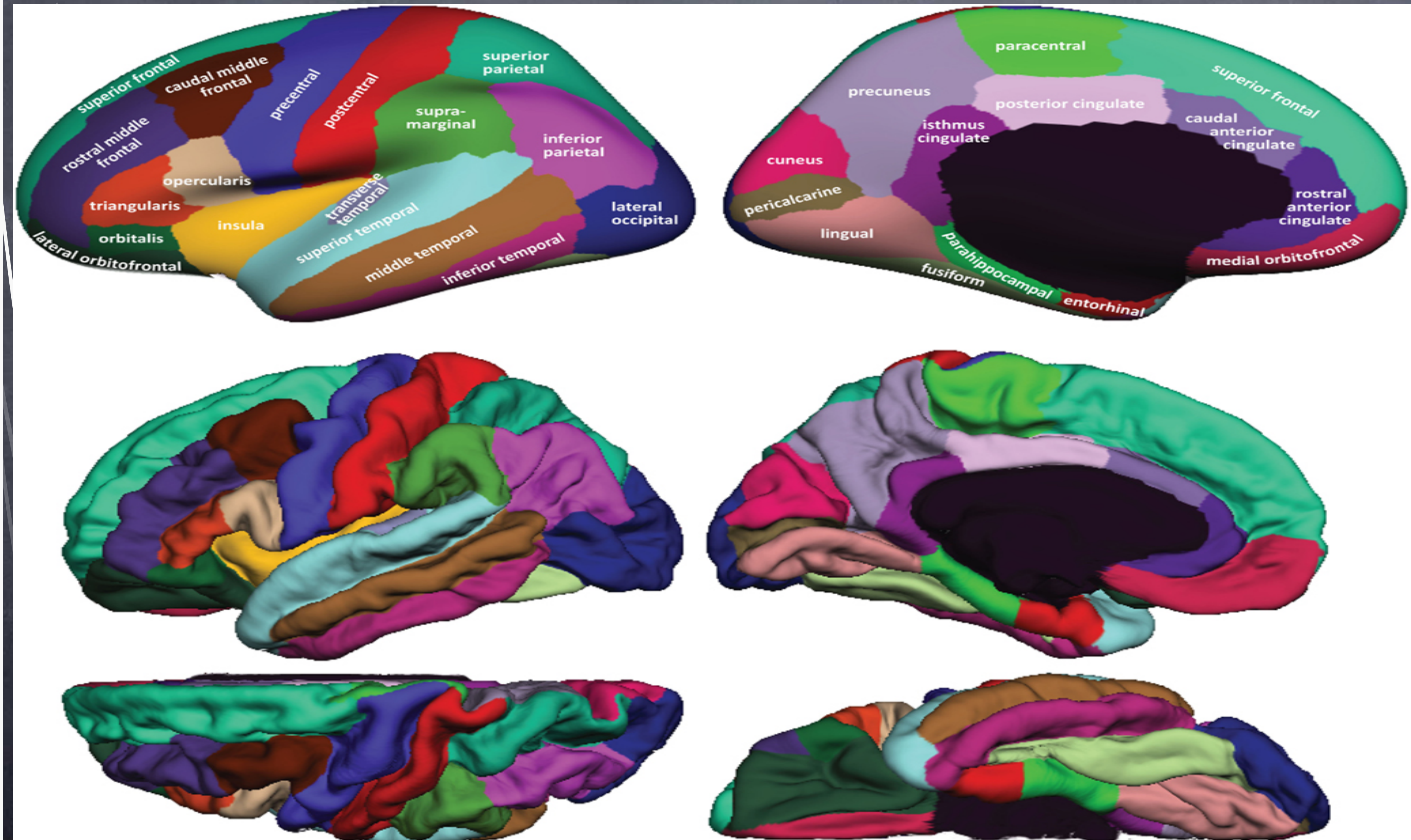
Friston et al. (2003)

Data Collection

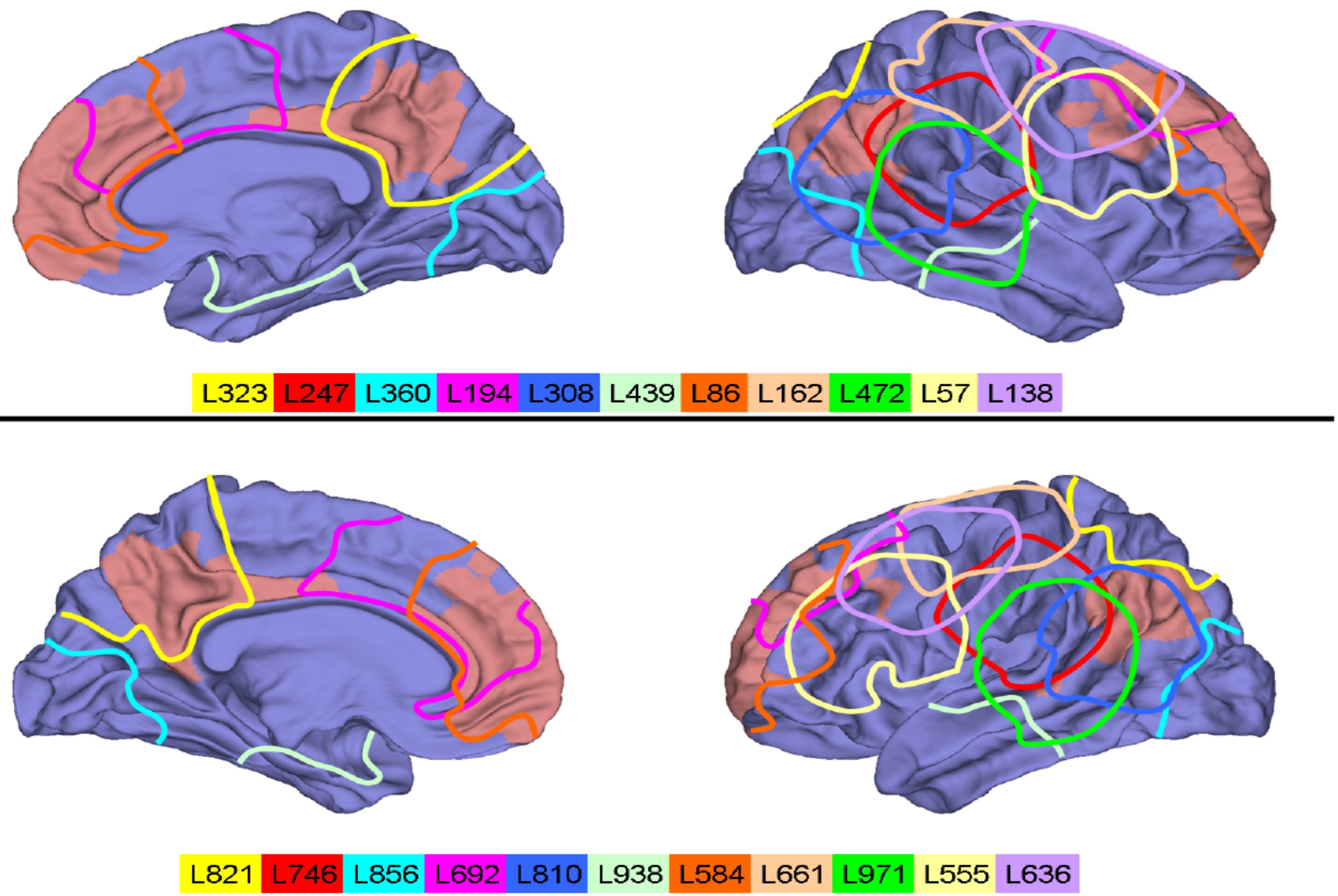
- 49 subjects
- Ages 18 – 82
- Resting state fMRI (3T scanner, single run, 22 mins, voxel size 3 x 3 x 3 mm)
- DTI (voxel size 2.3 x 2.3 x 2.3 mm)

Vattikonda et al. (2016) Neuroimage

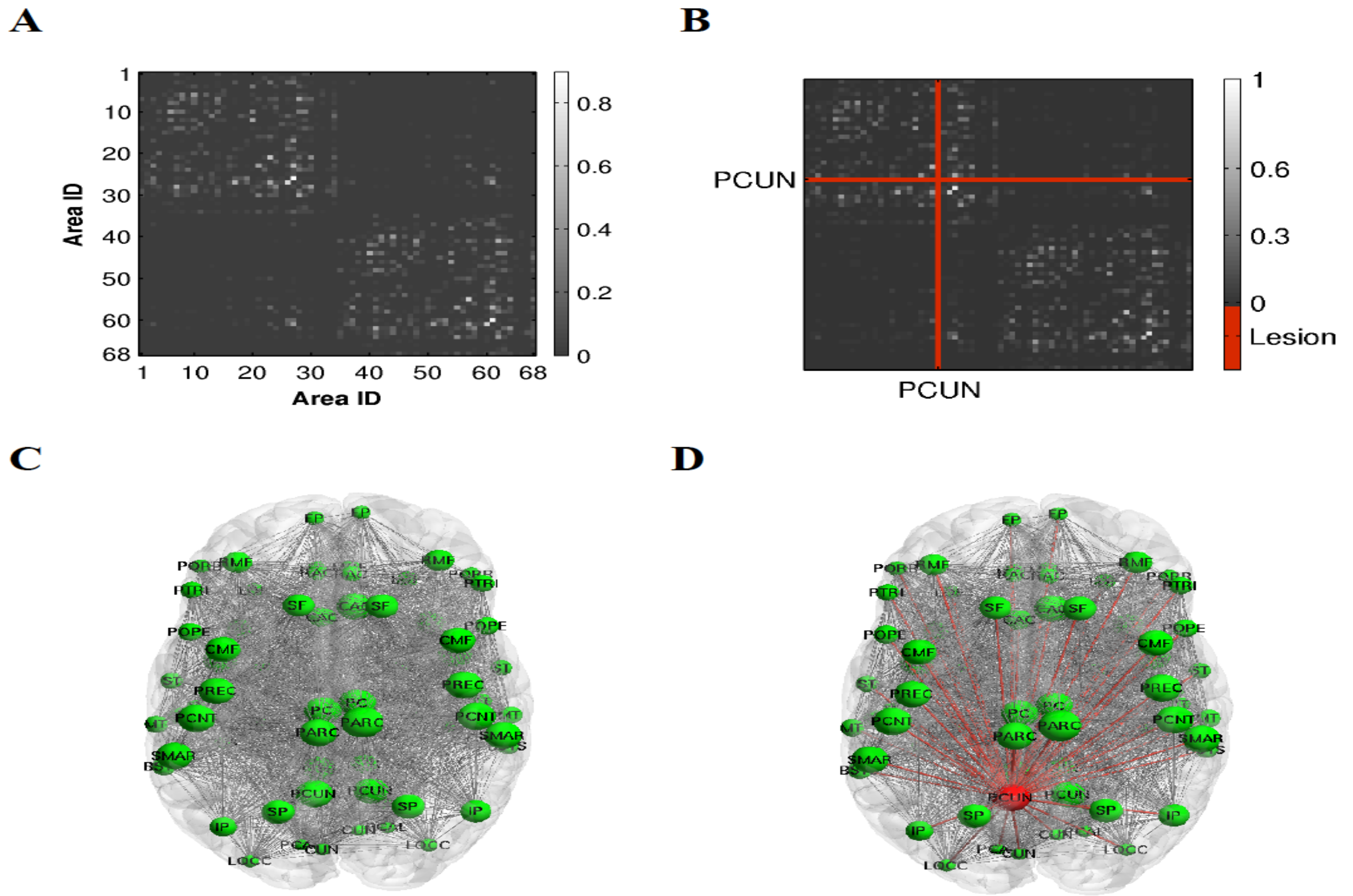
Parcellation of the cerebral cortex using DK Atlas



Lesion centers in the proximity of DMN



Generating *in-silico* focal leison



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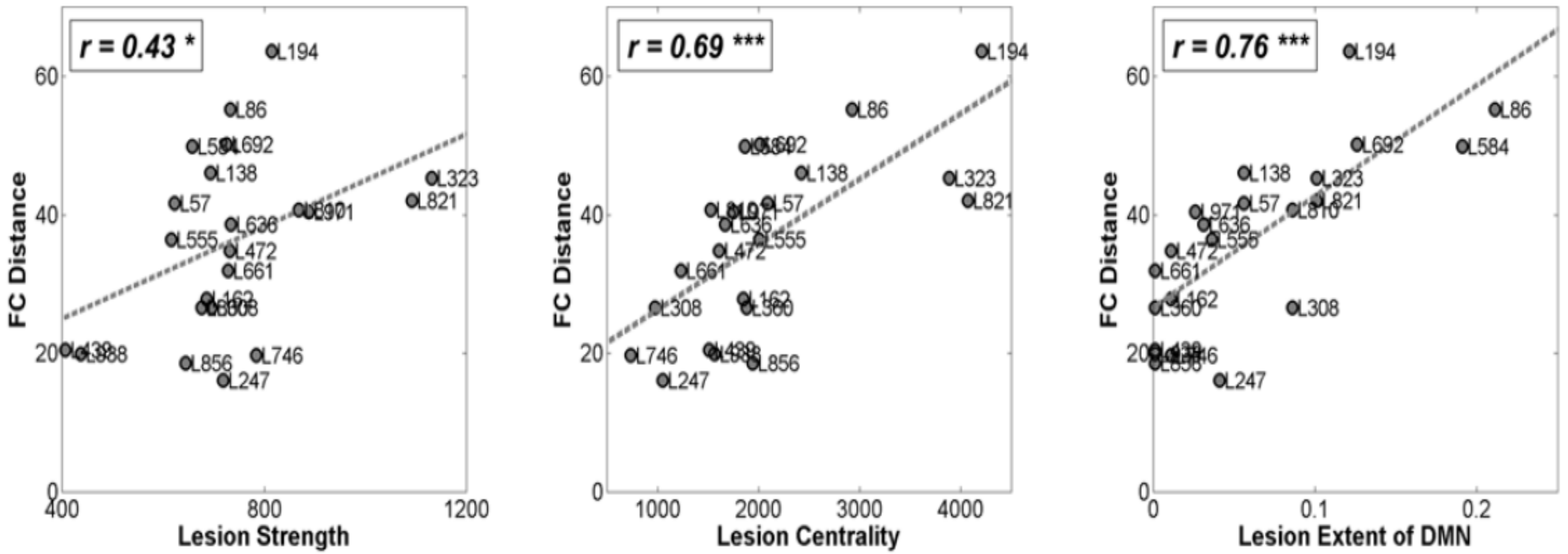
Lesion severity in the brain scales with lesion centrality and node strength

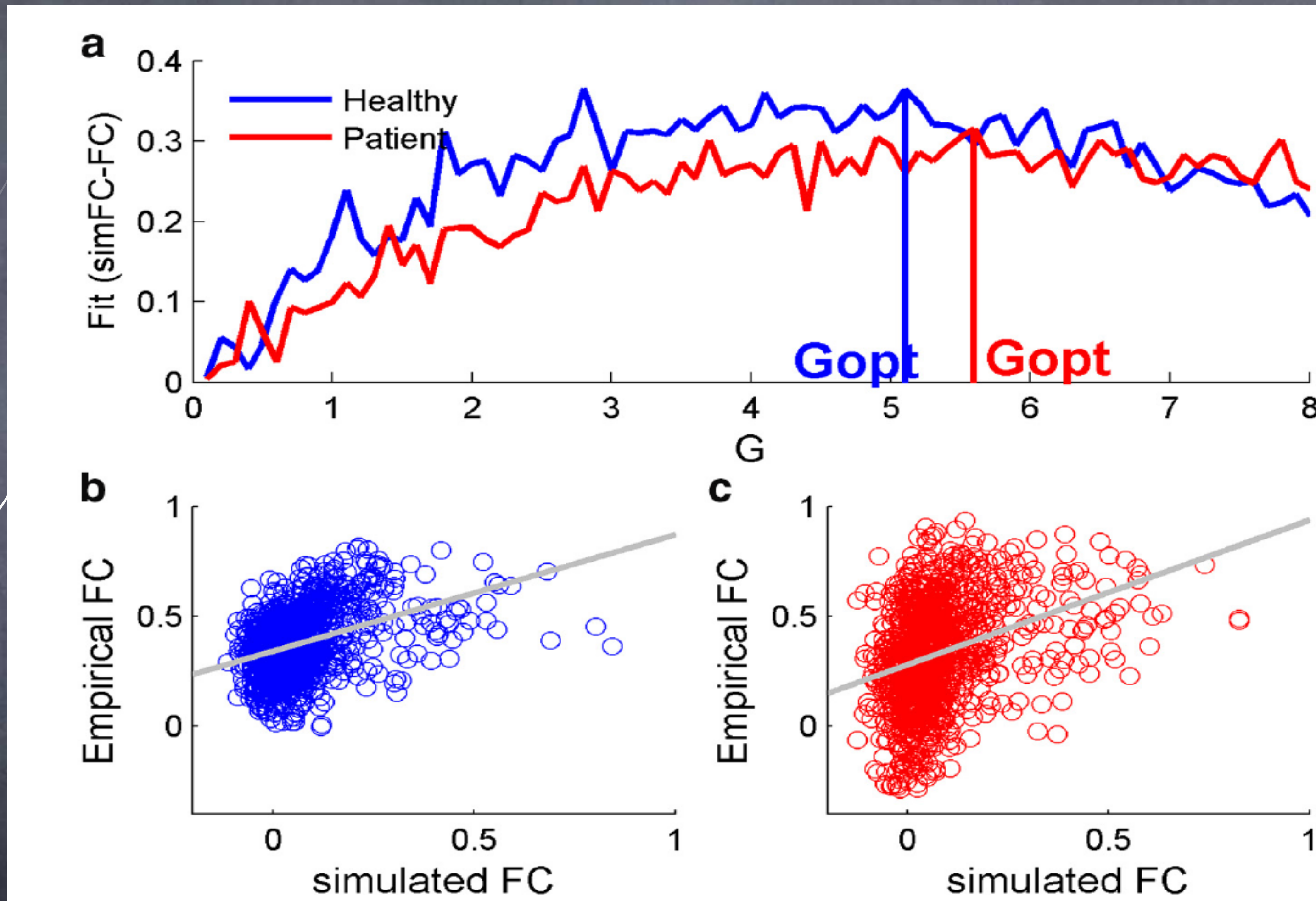


$$FCD = \sqrt{\sum_{i=1}^{N}\sum_{j=1}^{N}(FCEmpirical(i,j) - FCModel(i,j))^2}$$

$$Strength(area_i) = \sum_{j=1}^{N} C_{ij}$$

Alstott et al. PlosCompBio(2009)

Long range coupling between brain areas exhibit significant difference between patient and control

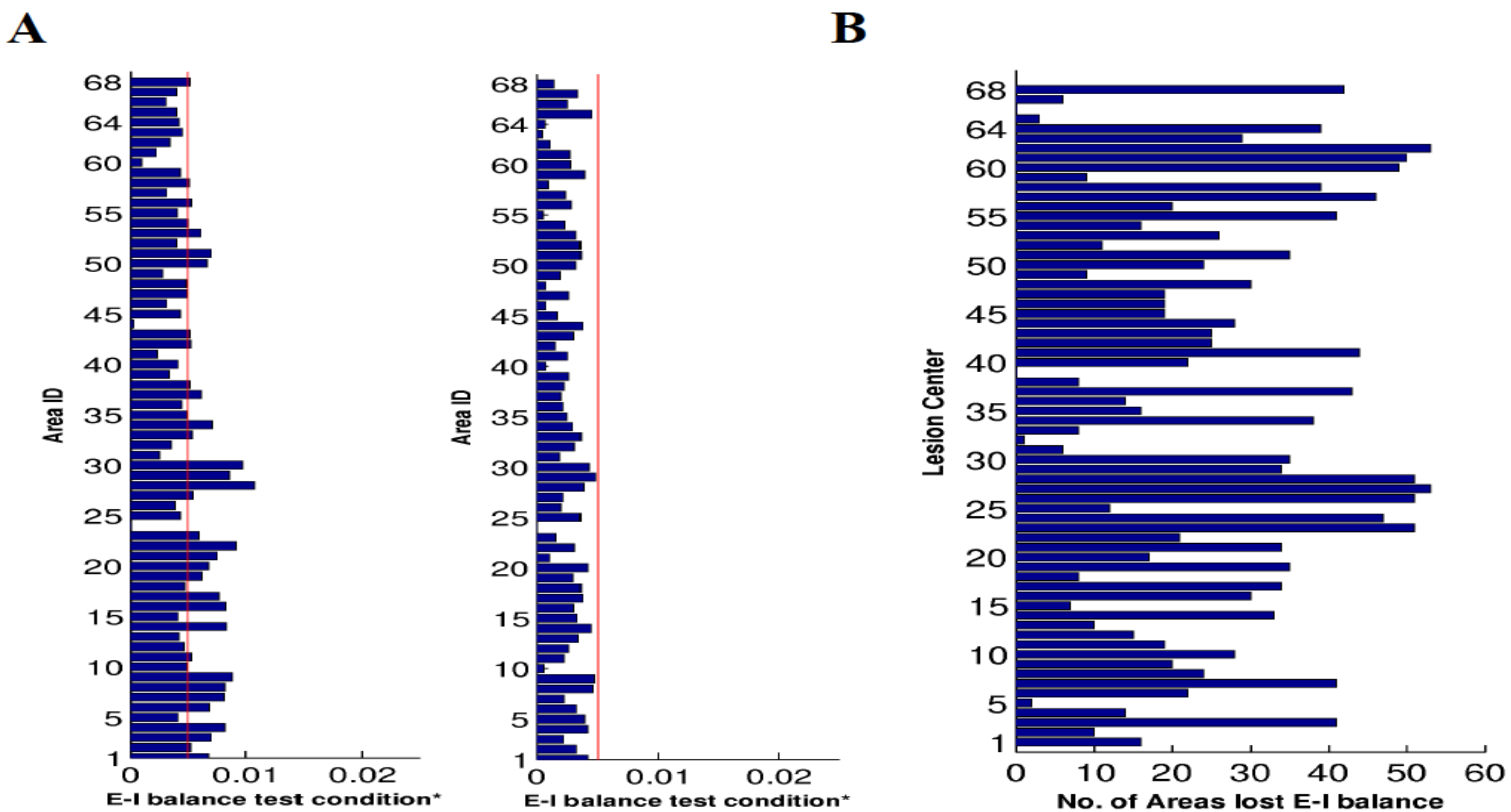


Adhikari et al.(2015) J.Neurosci,
Vattikonda et al. (2016) Neuroimage

Impact on excitation-inhibition balance based on the proximity to lesion center

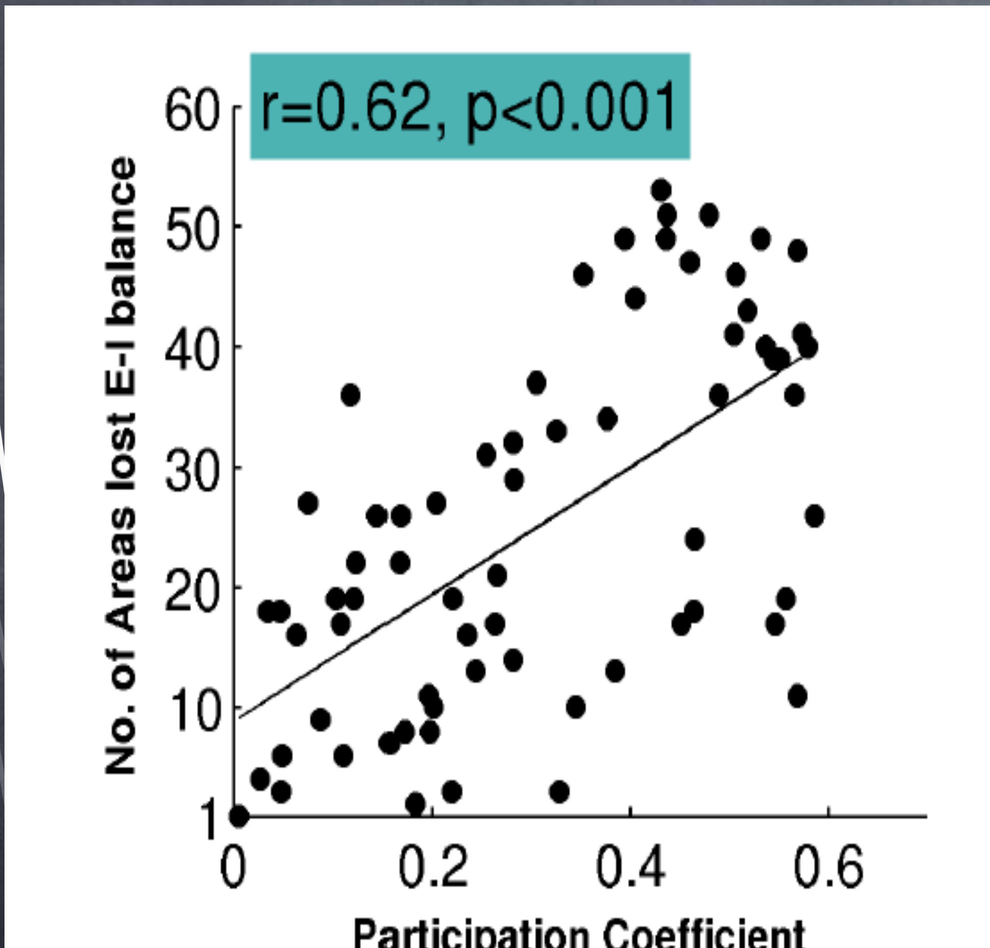
An area, say i, is considered to have E-I balance if:

$$I_i^E - \frac{b_E}{a_E} = -0.026 \text{ nA}, \text{ Tolerance: } \pm 0.005\text{nA}$$



Vattikonda et al. (2016) Neuroimage

Hub areas has the highest impact on areal E-I balance

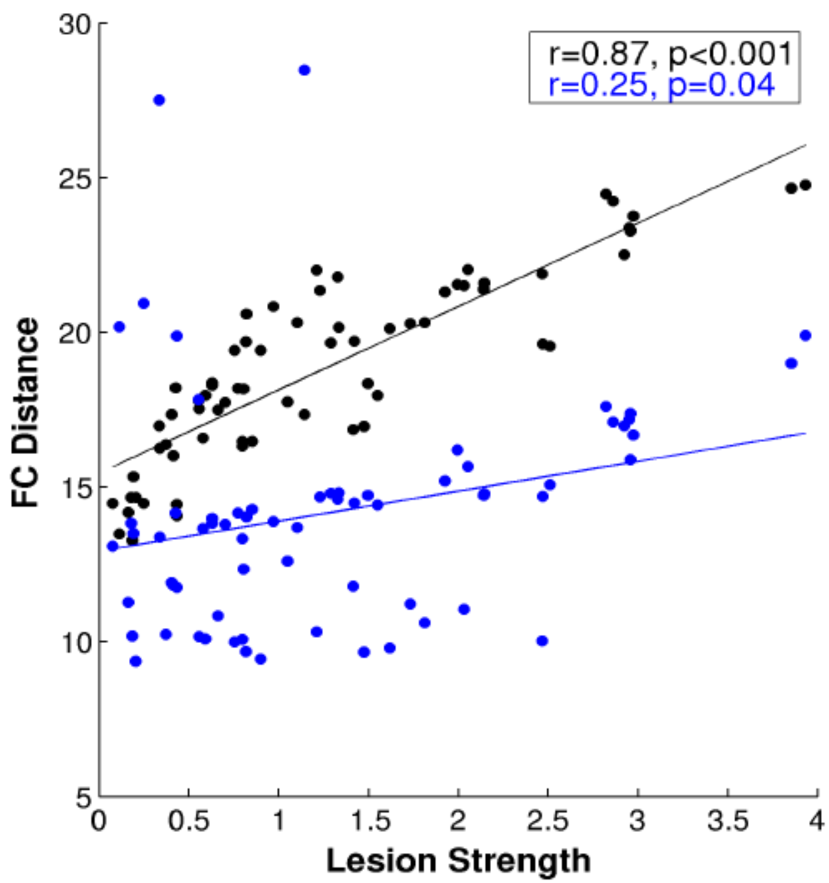


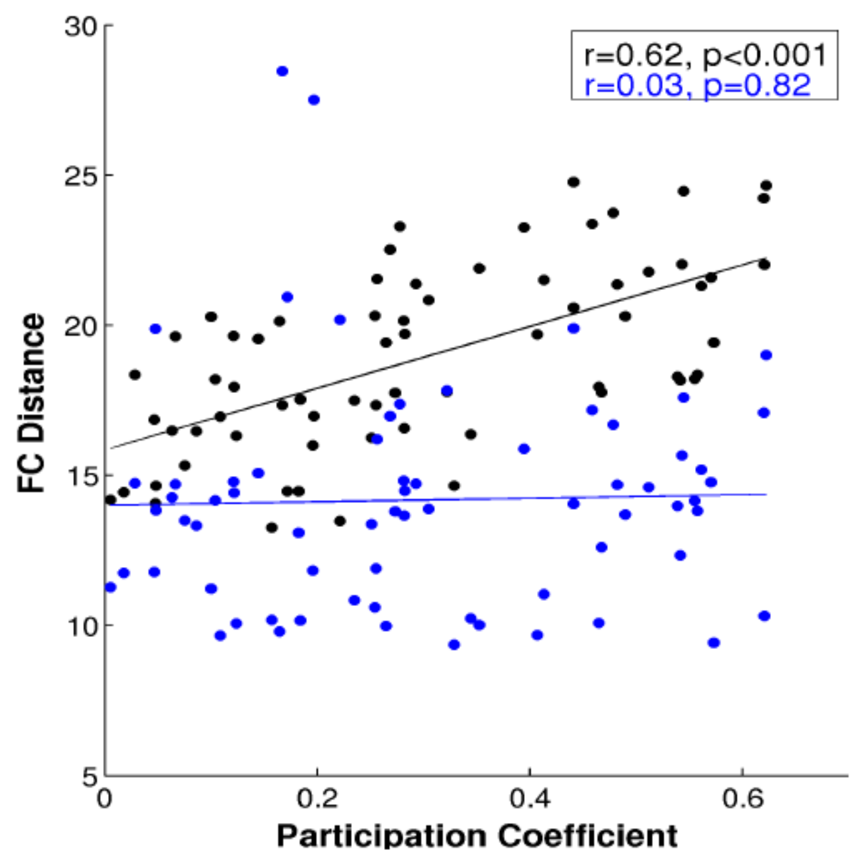
- We hypothesize that E-I balance is a potential underlying mechanism that is affected by lesions.
- Since homeostasis play a key role in proper function of neuronal circuits lesions at hubs have larger impact on function
- We found that when nodes with high participation coefficient are lesioned then there is a widespread disturbance in E-I balance.

Functional recovery independent of lesion center location with E-I balance

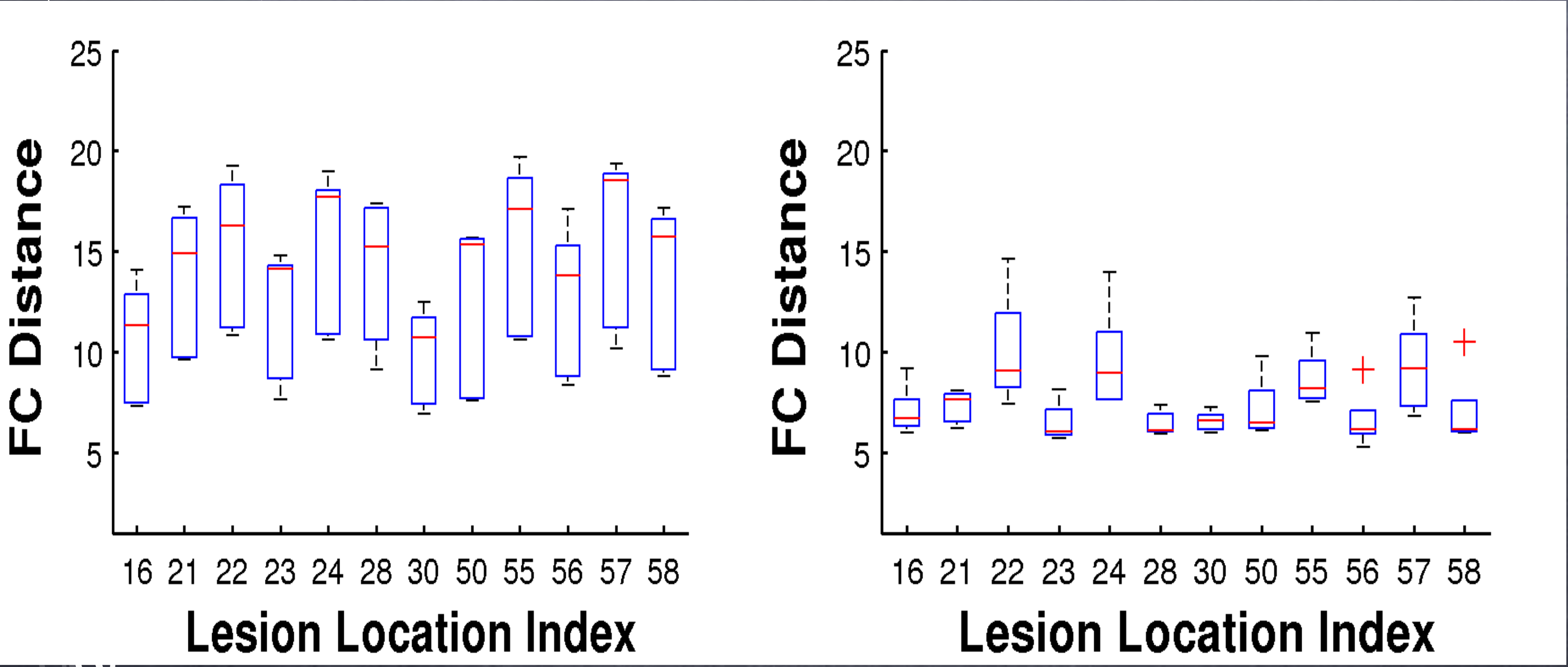
$$FCD = \sqrt{\sum_{i=1}^{N}\sum_{j=1}^{N}(FCEmpirical(i,j) - FCModel(i,j))^2}$$

$$P_i = 1 - \sum_{s=1}^{N_M}\left(\frac{k_{is}}{k_i}\right)$$





Functional recovery across subjects and location of lesion



Functional recovery estimates across variety of lesion centers

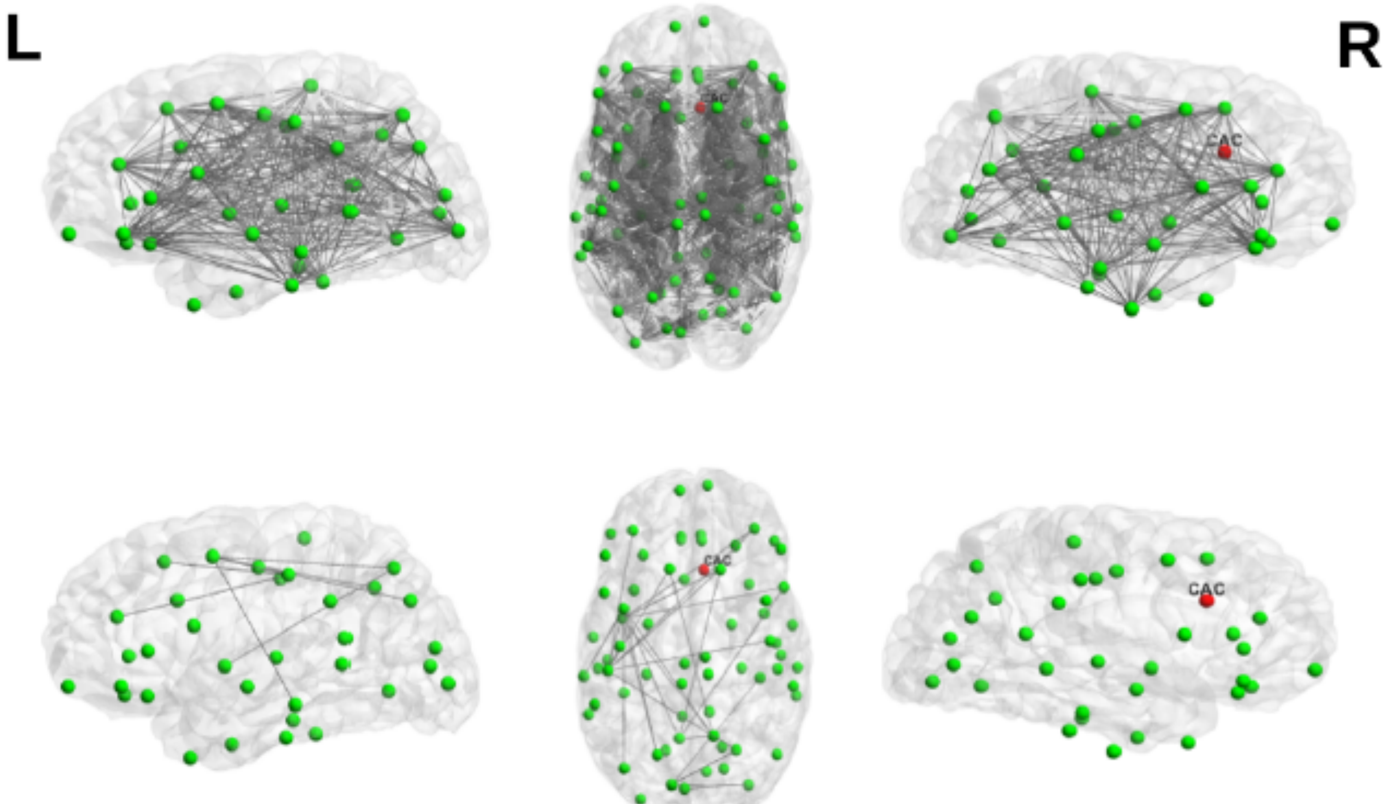
- Z-scores are used to test the hypothesis that whether the functional correlations of any pair of ROI before and after lesion are from different distributions.

$$Z_{ij} = \frac{(r_{ij}^{healthy} - r_{ij}^{lesioned})}{\sqrt{(\frac{1}{df-3} + \frac{1}{df-3})}}$$

- We have compared the z-scores before and after lesion with lesions located in cortical midline (CAC), frontal cortex (CMF) and parietal cortex (IP).

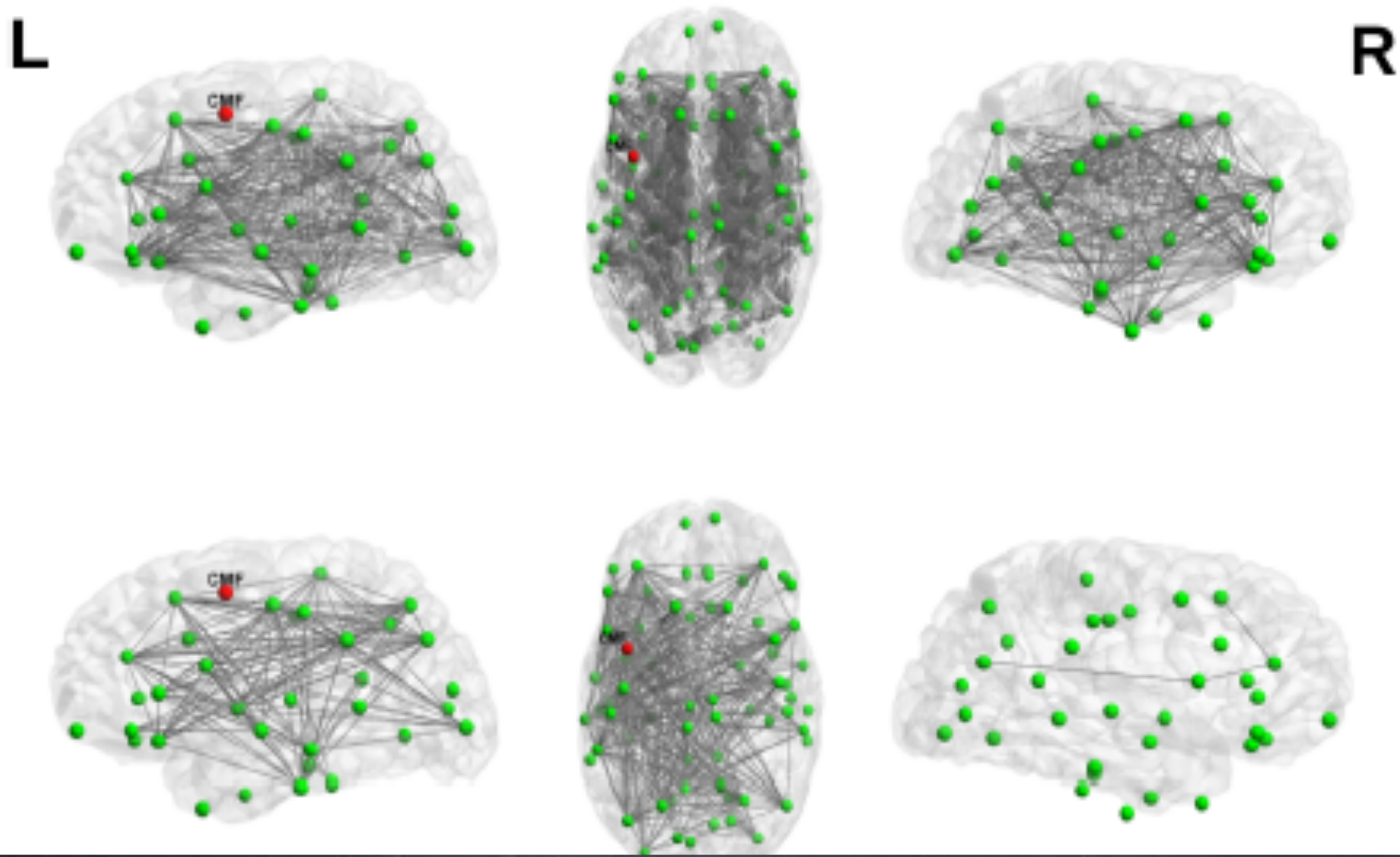
Functional recovery re-establsihing lost areal E-I balance

- With Lesion center as CAC, The number of connections that significantly changed within ipsilateral hemisphere is reduced by 97% and within contralateral hemisphere by 100%

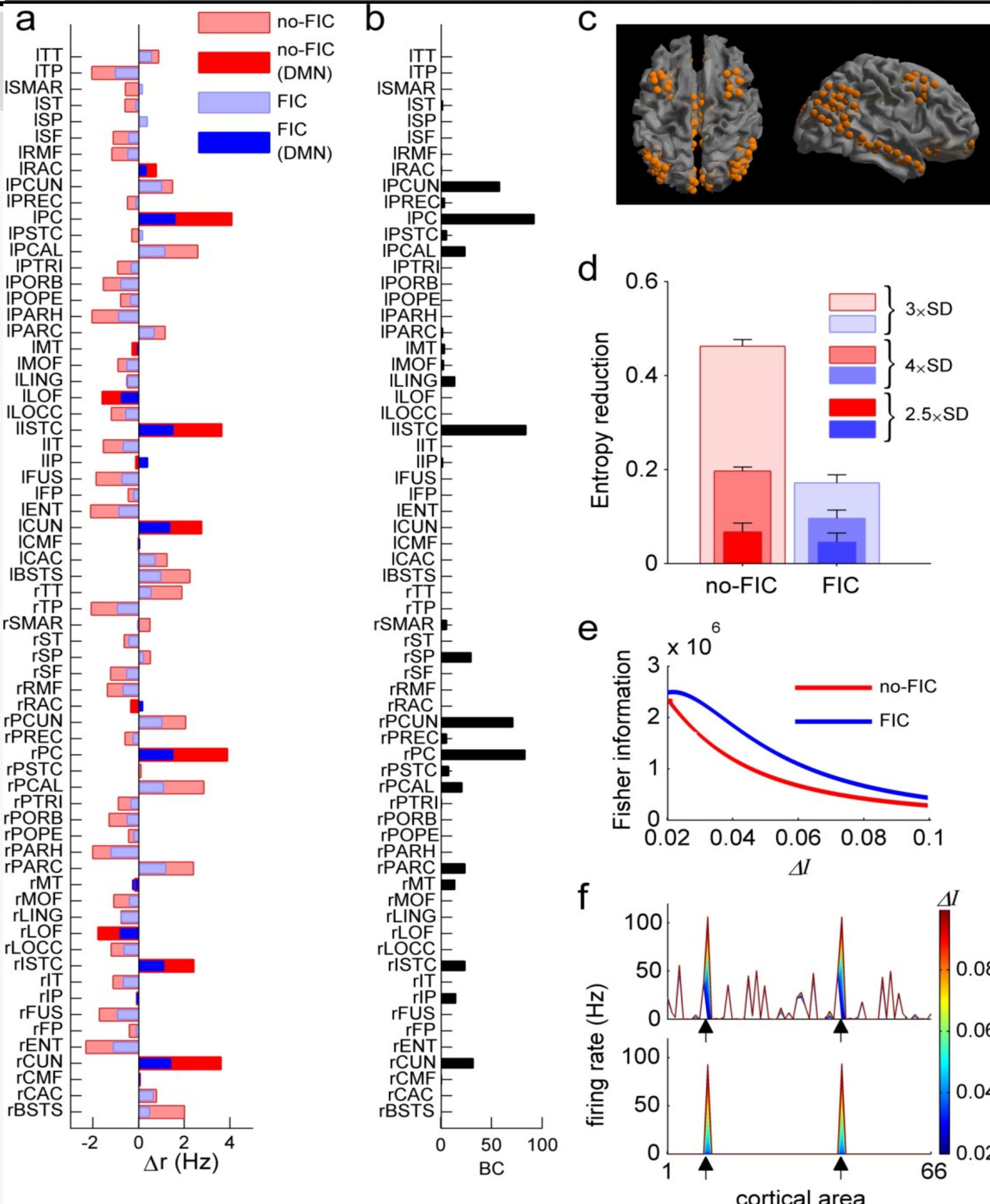


Impact of lesion hotspot on recovery

- With the lesion center as left CMF, The number of connections that significantly changed within ipsilateral hemisphere is reduced by 61% and within contralateral hemisphere by 99%



Outlook



- Regulating the local level of feedback inhibition in the brain has an important role at the global level:
- Inhibitory plascity attenuates the response of cortical areas in the default mode network and recovers FC on distant sites.
- Inhibitroy local regulation increases the information capacity of the global network by increasing the entropy of the network's evoked responses.
- Same mechanism increases the stimulus discriminability
- Discovery of optimal neuro-stimulation sites

Funding and support

This work is supported by Department of Biotechnology Govt. of India Ramalingaswami fellowship

I would like to thank collaborators Professor Bapi Raju (IIIT Hyderabad), Professor Gustavo Deco(UPF Barcelona), and Dr. Arpan Banerjee (NBRC, Delhi)

Department of Biotechnology Govt. of India

Department of Science and Technology Government of India

NNMCB National Network for Mathematical and Computational Biology

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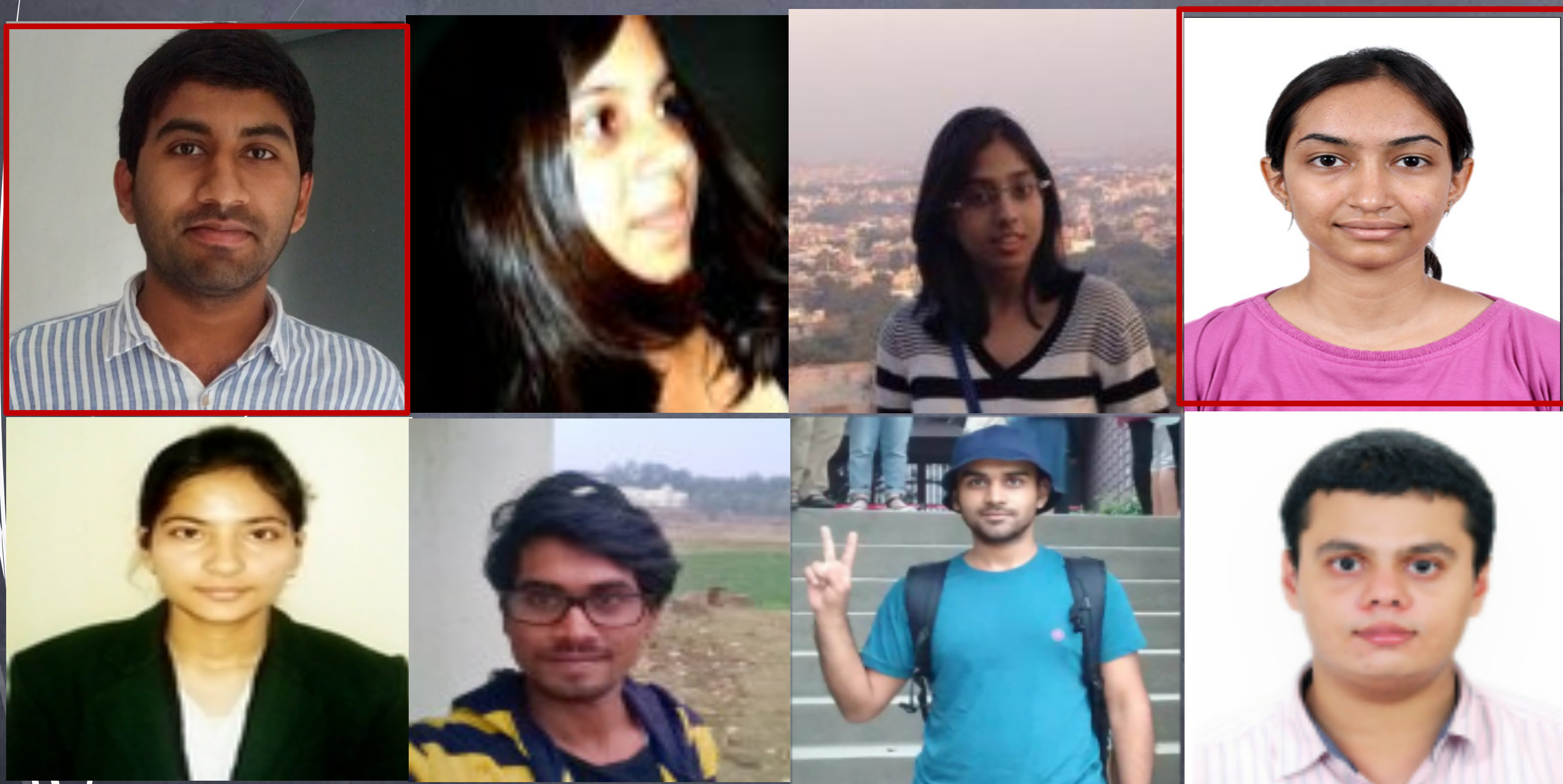
Contribution by students



Thank you