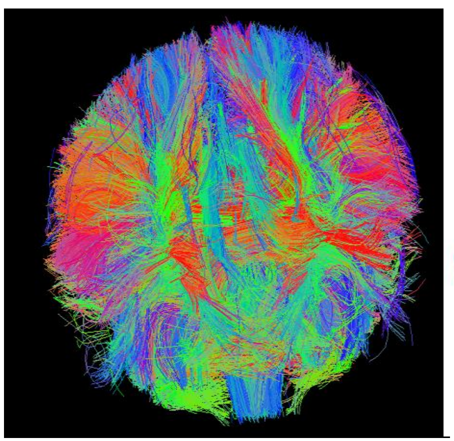
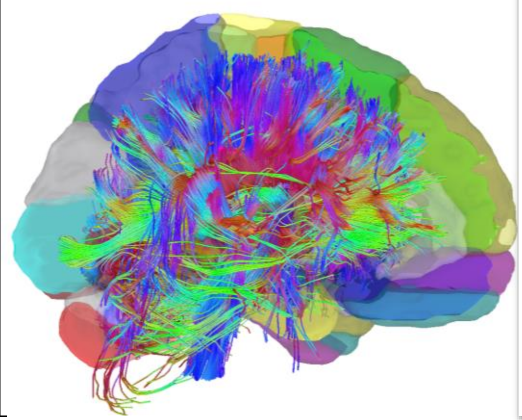
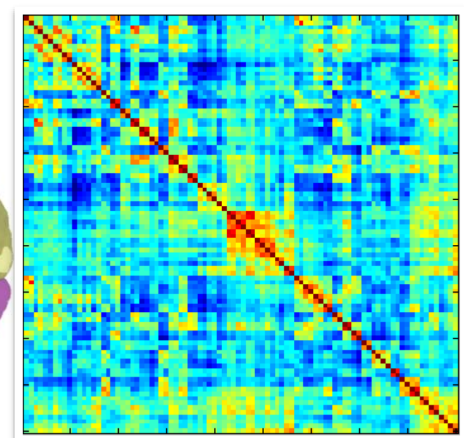
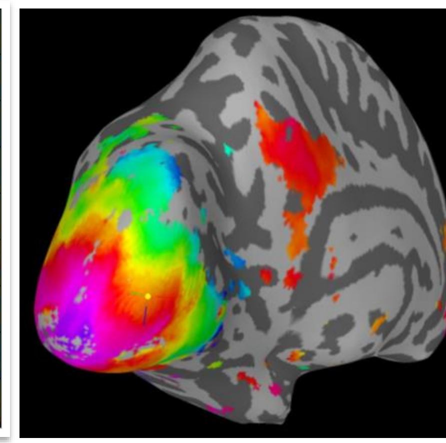
Exploring Human Brain Networks with Advanced MR Neuroimaging Technology

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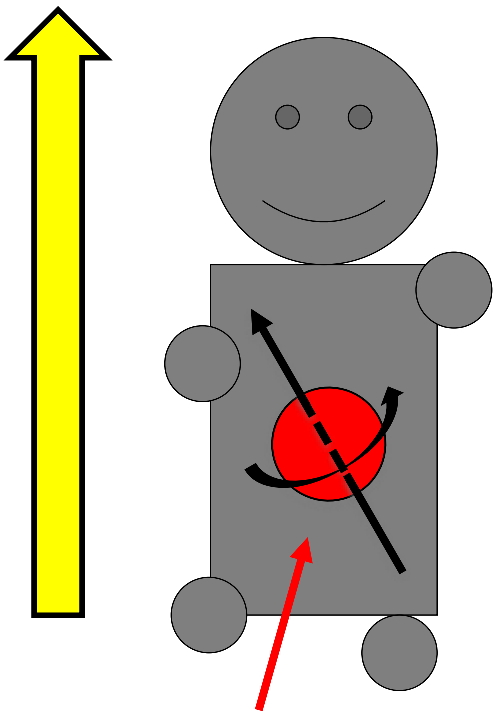
2018/6/27@BDHS

The theory of MRI

M *= Magnetic* ***R*** *= Resonance* ***I*** *= Imaging*

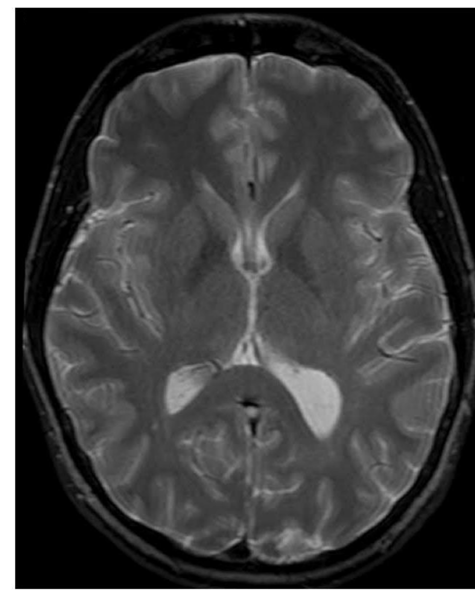
Magnetic field direction



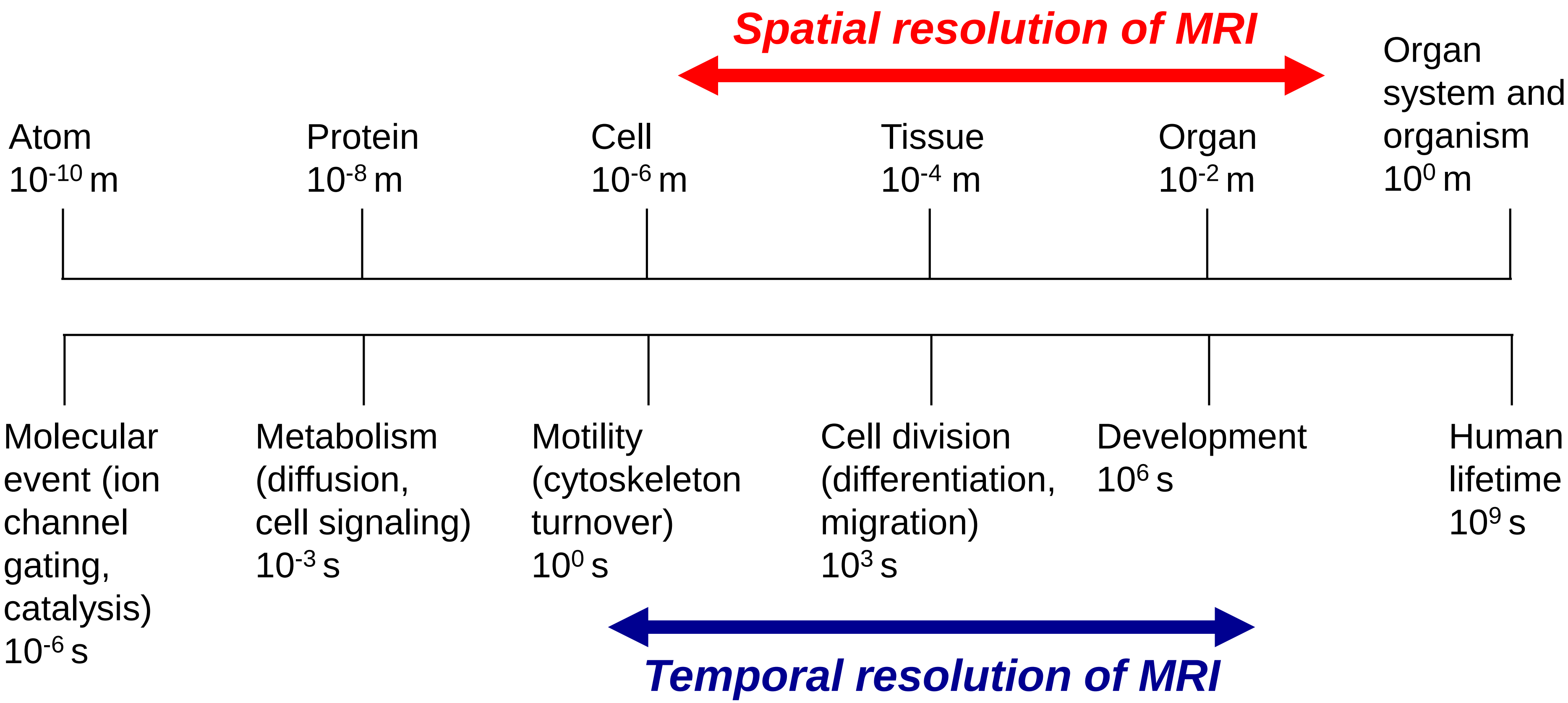
Proton: like a small magnet
Water: 70% of human body

Same frequency

1.5T MRI: 63.5 MHz;
3T MRI: 127 MHz



Spatial and temporal scales in biological systems



- Sporns, "Discovering the Human Connectome," p6.

Why MRI?

- Non-invasive (*safe and no harm*)
- Non-radioactive (*good for research*)
- Adequate spatial and temporal resolution for imaging biological tissues (*μm~mm, ms~s*)
- Quantitative physical/physiological contrasts (*spin density, relaxation time, susceptibility, perfusion, diffusion, flow velocity, temperature, etc …*)
- From animal to human (*good for translational research*)

How the advanced computational technology changes MRI?

- *With the advancement of computational power and methodology, the development of MRI technology has been revolutionized during the past few year*

DATA ACQUISITION → ***IMAGE PROCESSING*** → ***DATA ANALYSIS***

DATA ACQUISITION
- Faster scan
- Higher throughput
- Multi-parametric contrast manipulation

IMAGE PROCESSING
- Undersampled data recon.
- Denoising
- Resolution enhancement
- Segmentation

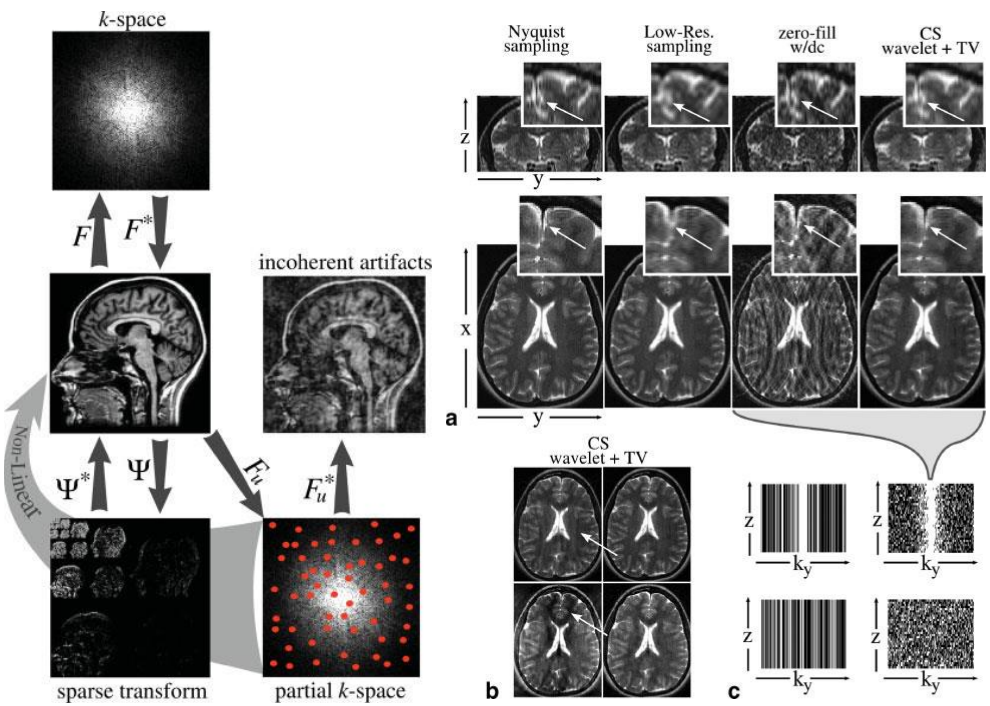
DATA ANALYSIS
- Multi-modal parametric training and model establishment
- Classification
- Prediction

Data Acquisition

Magnetic Resonance in Medicine 58:1182–1195 (2007)

Sparse MRI: The Application of Compressed Sensing for Rapid MR Imaging

Michael Lustig,[1*] David Donoho,[2] and John M. Pauly[1]



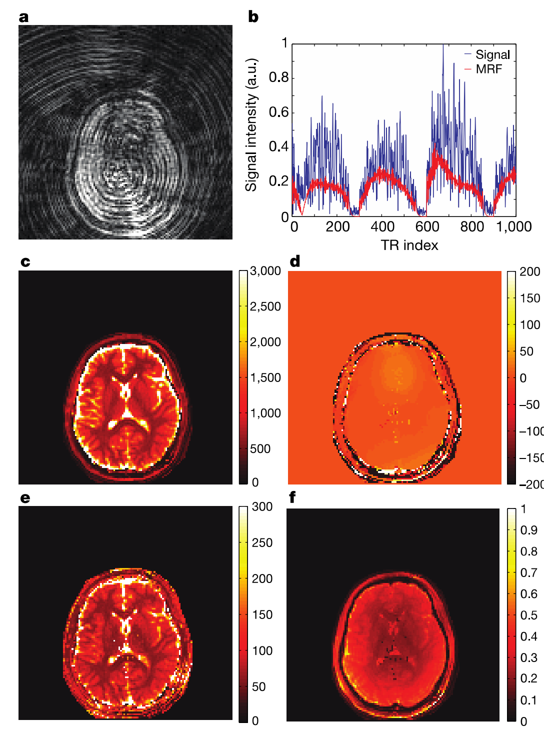
- Lustig et al., Mag Reson Med 2007

ARTICLE

doi:10.1038/nature11971

Magnetic resonance fingerprinting

Dan Ma[1], Vikas Gulani[1,2], Nicole Seiberlich[1], Kecheng Liu[3], Jeffrey L. Sunshine[2], Jeffrey L. Duerk[1,2] & Mark A. Griswold[1,2]



- Ma et al., Nature 2013

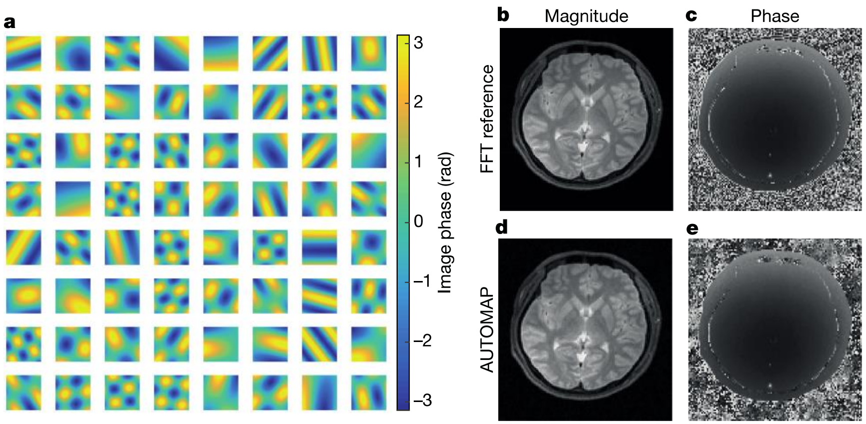
Image Processing

LETTER

doi:10.1038/nature25988

Image reconstruction by domain-transform manifold learning

Bo Zhu[1,2,3], Jeremiah Z. Liu[4], Stephen F. Cauley[1,2], Bruce R. Rosen[1,2] & Matthew S. Rosen[1,2,3]



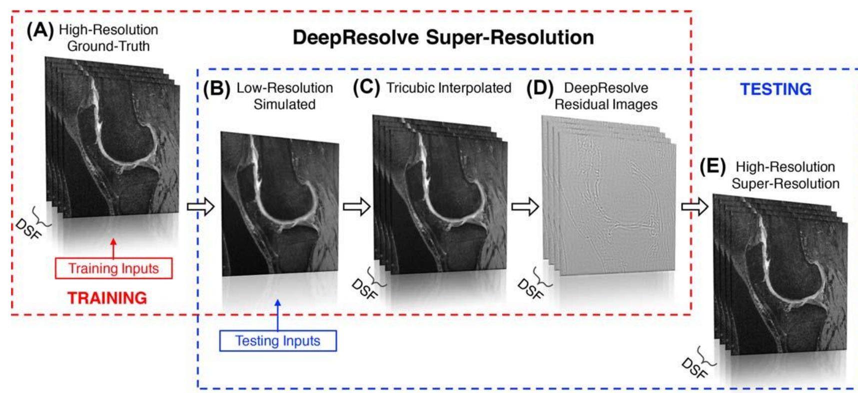
Received: 16 December 2017 | Revised: 14 February 2018 | Accepted: 22 February 2018
DOI: 10.1002/mrm.27178

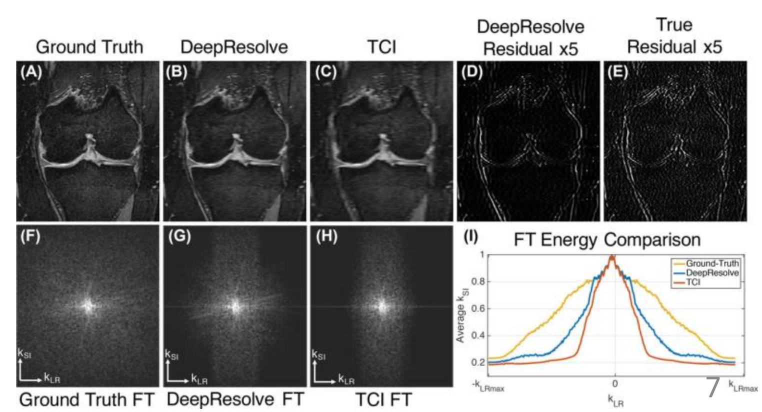
FULL PAPER

Magnetic Resonance in Medicine

Super-resolution musculoskeletal MRI using deep learning

Akshay S. Chaudhari[1,2*] | Zhongnan Fang[3*] | Feliks Kogan[1] | Jeff Wood[1] | Kathryn J. Stevens[1,4] | Eric K. Gibbons[5] | Jin Hyung Lee[2,3,6,7] | Garry E. Gold[1,2,4] | Brian A. Hargreaves[1,2,7]





- Zhu et al., Nature 2018
- Chaudhari et al., Mag Reson Med 2017

Data Analysis

NeuroImage 101 (2014) 569–582

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis

Heung-Il Suk [a], Seong-Whan Lee [b], Dinggang Shen [a,b,*], the Alzheimer's Disease Neuroimaging Initiative [1]

[a] Department of Radiology and Biomedical Research Imaging Center (BRIC), University of North Carolina at Chapel Hill, NC, USA
[b] Department of Brain and Cognitive Engineering, Korea University, Seoul, Republic of Korea

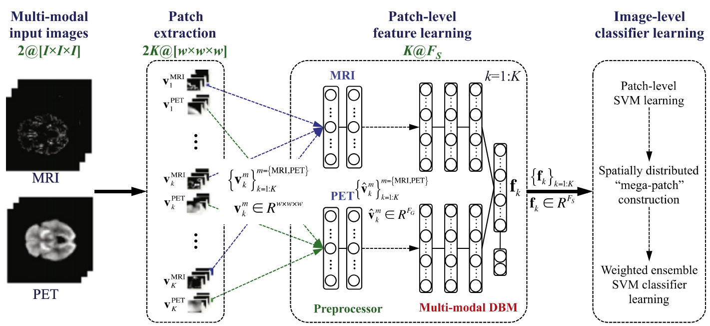


Table 2
A summary of the performances of two methods. The boldface denotes the best performance in each metric for each classification task.

	Method	Modality	ACC (%)	SEN (%)	SPEC (%)	BAC (%)	PPV (%)	NPV (%)	AUC (%)
AD/NC	Liu et al.	MRI	90.18 ± 5.25	91.54	90.61	91.08	88.94	90.67	0.9620
		PET	89.13 ± 6.81	90.06	89.36	89.71	88.49	89.26	0.9594
		MRI + PET	90.27 ± 7.02	89.48	92.44	90.96	90.56	88.70	0.9655
	Proposed	MRI	92.38 ± 5.32	91.54	94.56	93.05	92.65	90.84	0.9697
		PET	92.20 ± 6.70	88.04	**96.33**	92.19	95.03	89.66	0.9798
		MRI + PET	**95.35 ± 5.23**	**94.65**	95.22	**94.93**	**96.80**	**95.67**	**0.9877**
MCI/NC	Liu et al.	MRI	81.00 ± 4.98	97.08	48.18	72.63	79.14	88.99	0.8352
		PET	81.14 ± 10.22	96.03	52.59	74.31	80.26	84.16	0.8231
		MRI + PET	83.90 ± 5.80	98.97	52.59	75.78	81.18	97.22	0.8301
	Proposed	MRI	84.24 ± 6.26	**99.58**	53.79	76.69	81.23	**98.75**	0.8478
		PET	84.29 ± 7.22	98.69	56.87	77.78	81.99	94.57	0.8297
		MRI + PET	**85.67 ± 5.22**	95.37	**65.87**	**80.62**	**85.02**	89.00	**0.8808**
MCI-C/MCI-NC	Liu et al.	MRI	64.75 ± 14.83	22.22	89.57	55.90	46.29	77.39	0.6355
		PET	67.17 ± 13.43	40.02	82.61	61.32	64.13	70.31	0.6911
		MRI + PET	73.33 ± 12.47	33.25	**97.52**	65.38	80.00	73.18	0.7159
	Proposed	MRI	72.42 ± 13.09	36.70	90.98	63.84	65.49	**77.84**	0.7342
		PET	70.75 ± 13.23	25.45	96.55	61.00	75.00	70.69	0.7215
		MRI + PET	**75.92 ± 15.37**	**48.04**	95.23	**71.63**	**83.50**	74.33	**0.7466**

NeuroImage: Clinical 13 (2017) 361–369

Contents lists available at ScienceDirect

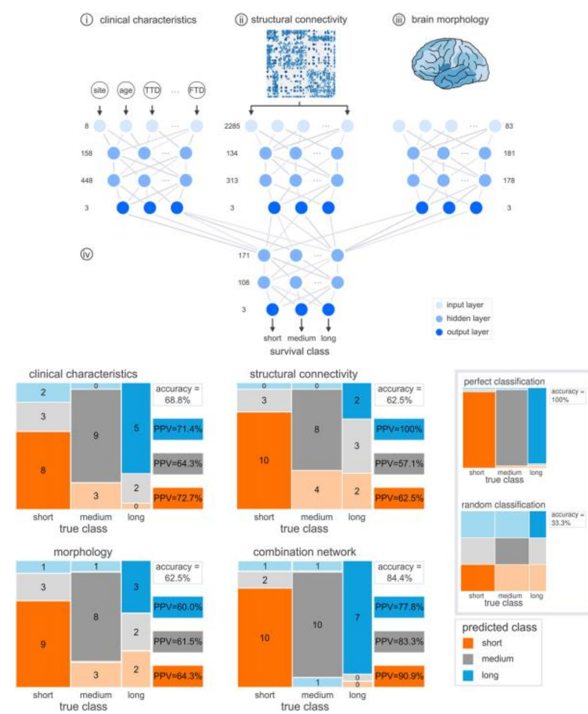
NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Deep learning predictions of survival based on MRI in amyotrophic lateral sclerosis

Hannelore K. van der Burgh [a], Ruben Schmidt [a], Henk-Jan Westeneng [a], Marcel A. de Reus [b], Leonard H. van den Berg [a,1], Martijn P. van den Heuvel [b,*,1]

[a] Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA, Utrecht, Netherlands
[b] Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3508 GA, Utrecht, Netherlands



- Suk et al., NeuroImage 2014; van der Burgh et al., NeuroImage: Clinical 2017

Target

Brain Connectomics & Connective Network

Approaches

MR Neuroimaging

Computational Analysis

Hardware Improvement

Applications

Cognitive Neuroscience, e.g. vocal emotion, cultural adaptation

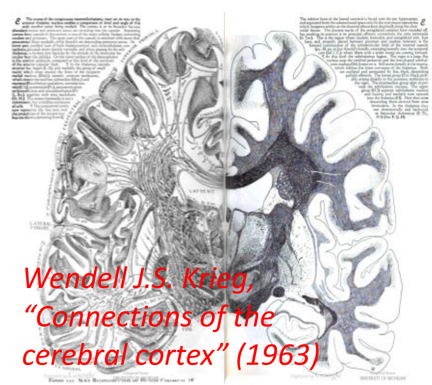
Neurological Diseases, e.g. stroke, traumatic brain injury, dementia

Psychiatric Disorders, e.g. depression, addiction

Why Brain Research?

A Challenging Target in 21st Century

- **The research of "brain and mind" can help us understand how brain works and improve the diagnosis or treatment for brain diseases**
- **Non-invasive neuroimaging technologies can provide accurate and reproducible measurements of brain structures and functions**

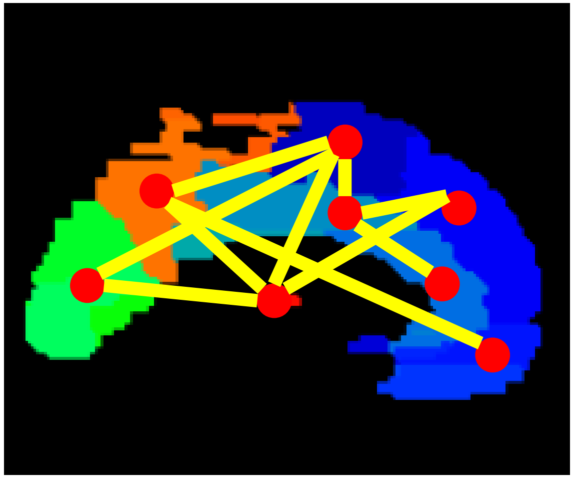


Wendell J.S. Krieg, "Connections of the cerebral cortex" (1963)

Scientific American, Nov 2008

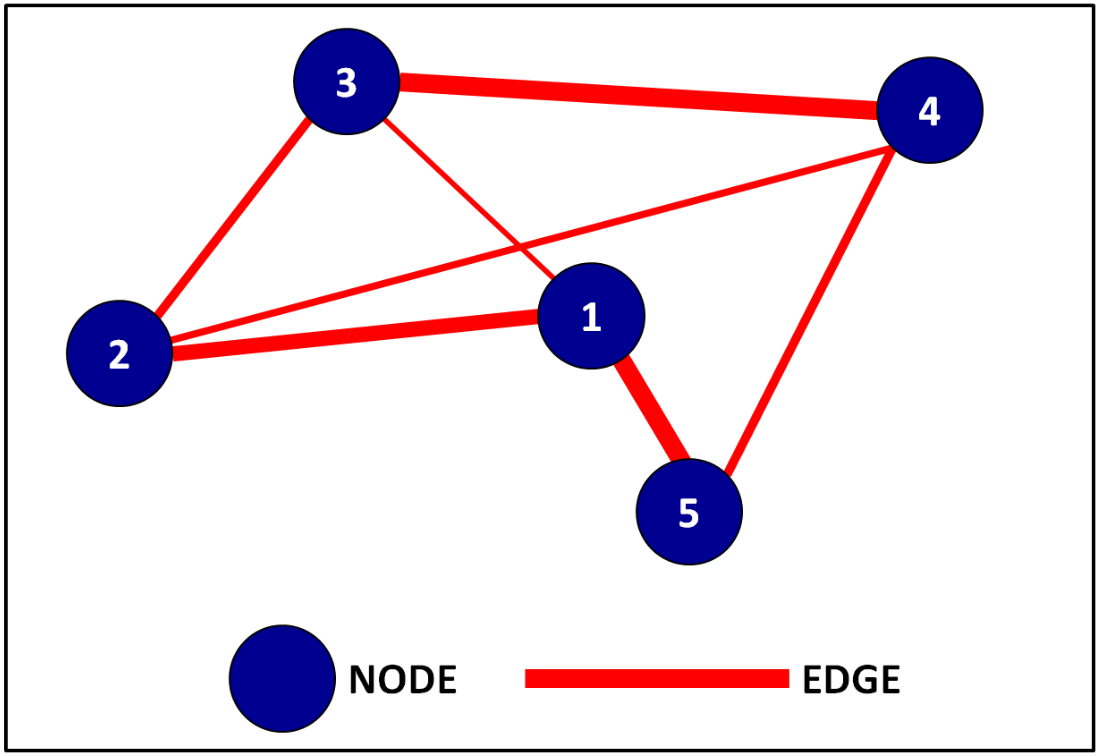
“Connectome” at Multiple Scales

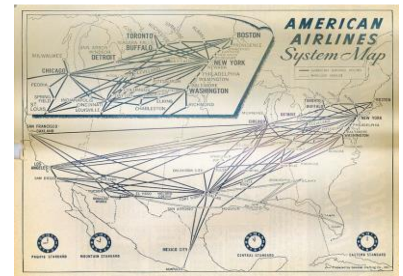
- **Brain connectome can be defined at different levels of scales, i.e. spatial resolution**
  - *Microscale: cellular level (neurons and synapses)*
  - *Mesoscale: circuits and cell populations*
  - *Macroscale: anatomical regions and pathways*
- ***Structural connectome*** and ***functional connectome*** (Sporns et al., 2005; Biswal et al., 2010; Bullmore and Sporns, 2009)



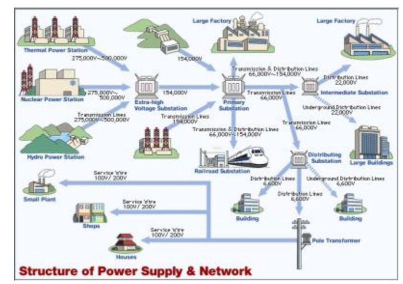
Measurement	***Edge representation***	***Empirical techniques***
Structural connectivity	*Presence/absence of physical links*	*Tract tracing, diffusion MRI, anatomical MRI*
Functional connectivity	*Statistical relationships between neural time courses*	*Neurophysiological recordings, EEG/MEG, BOLD fMRI*

What is a "Network"?





Airway



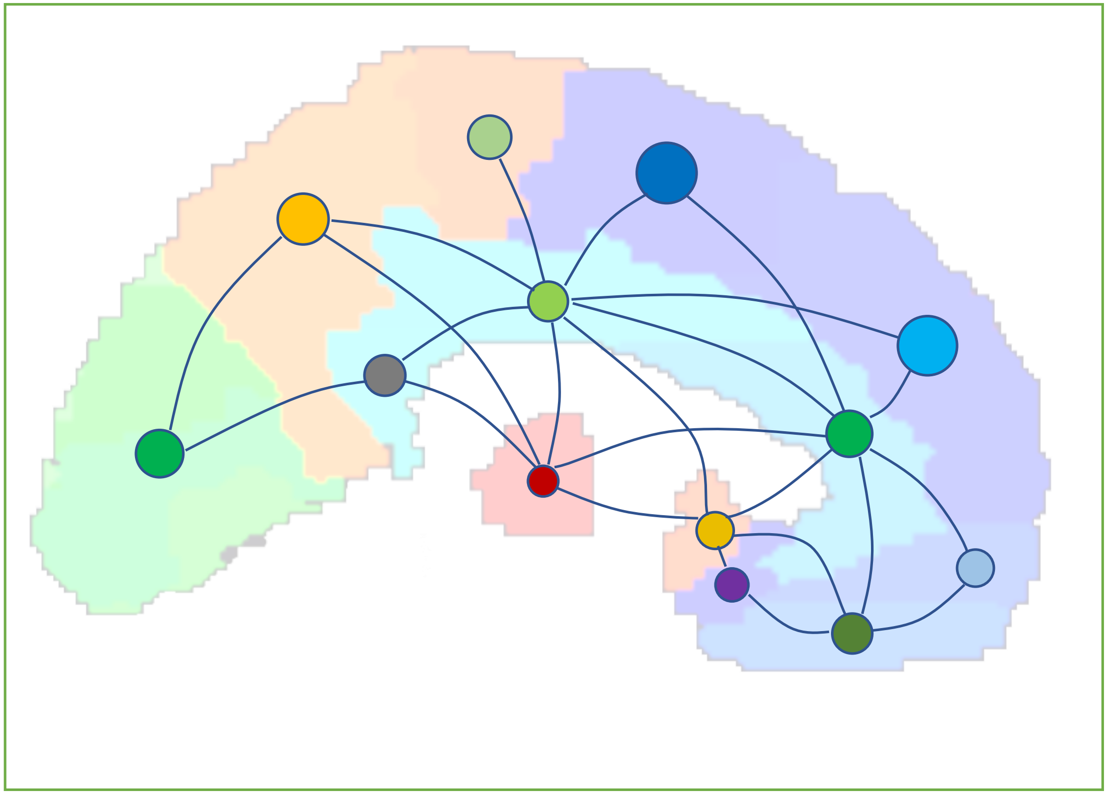
Electricity

Social

Two important issues:

- **How these nodes connect (structural connectivity)**
- **What happens between nodes (functional connectivity)**

Node *and* ***Edge*** *for representing a Brain Network*



Node –

Anatomical regions

Edge –

Structural connectivity

Functional connectivity

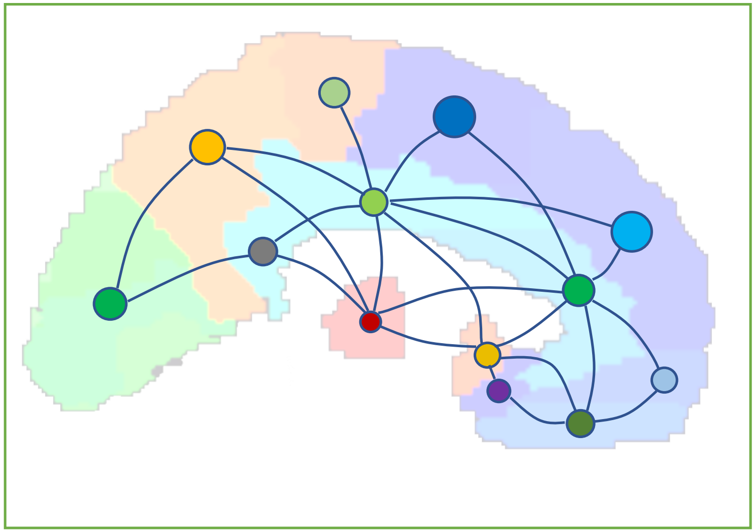
The basic concept is to compute nodes/edges from MRI data and measure the network characteristics of brain

How do we define the nodes of a brain network?

To define the “Nodes”

- *Network “**nodes**” can be represented by a group of cortical parcellations*

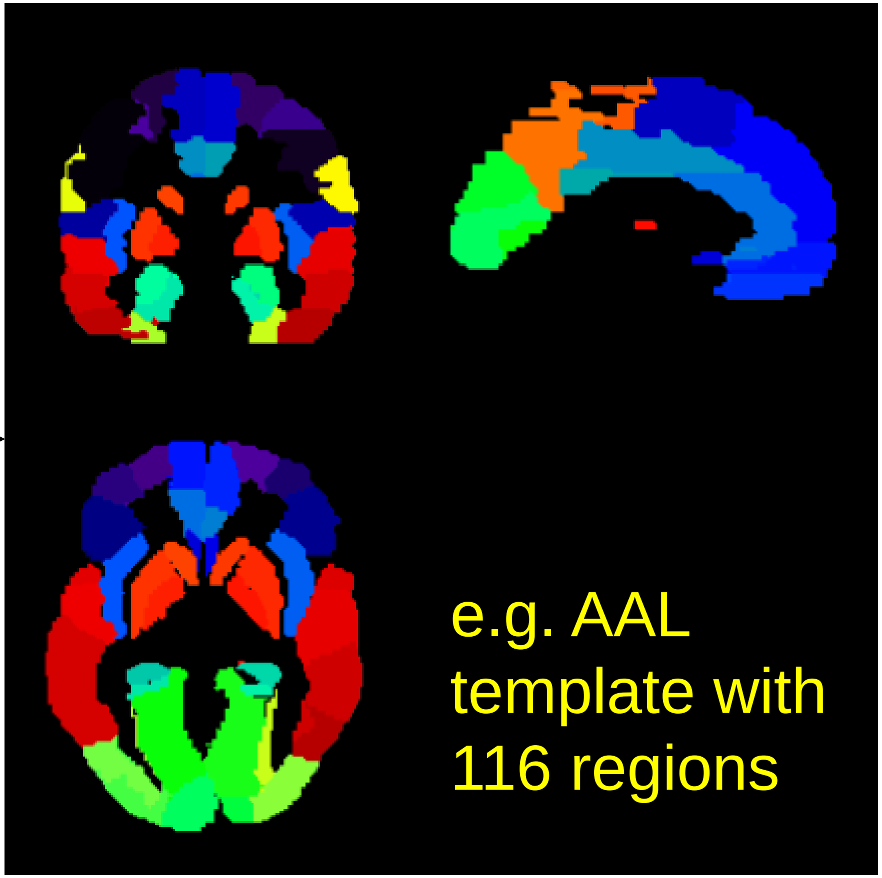
- *These cortical parcellations can be obtained by the following constraints*
  - ***Anatomical regions***
  - ***Structural connections***
  - ***Functional connectivity***



We can easily get the “Nodes” from a brain anatomical atlas

Subject’s 3DT1 anatomical images

Registration to template



How do we measure the structural connectivity?

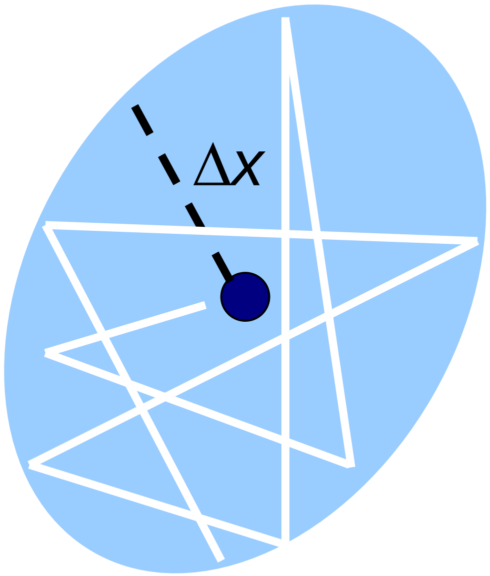
Diffusion phenomena

Microscopic random motion, i.e. Brownian motion

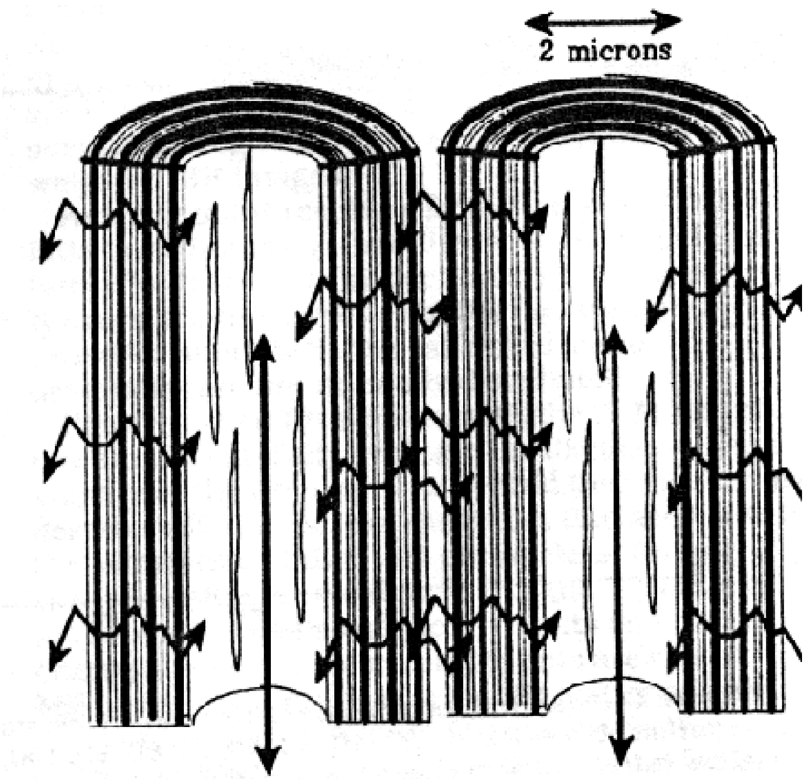
<u>To measure diffusion using MRI</u>

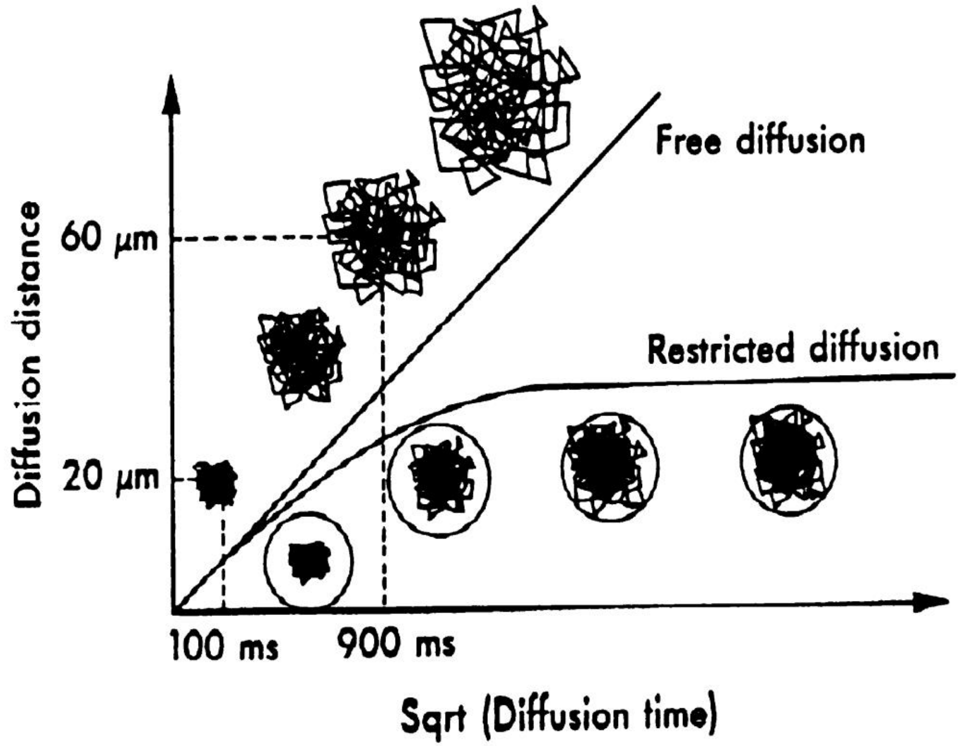
- **Pulsed gradient spin echo (PGSE)**
    - *Stejskal and Tanner, 1965*
- **Diffusion-weighted imaging (DWI)**
    - *Wesbey et al., 1984*
- **Diffusion tensor imaging (DTI)**
    - *Basser et al., 1994*
- **Diffusion spectrum imaging (DSI)**
    - *Wedeen et al., 2000*

$$\Delta x = \sqrt{2D\Delta t}$$



Diffusion anisotropy in biological tissue, e.g. neural fibers



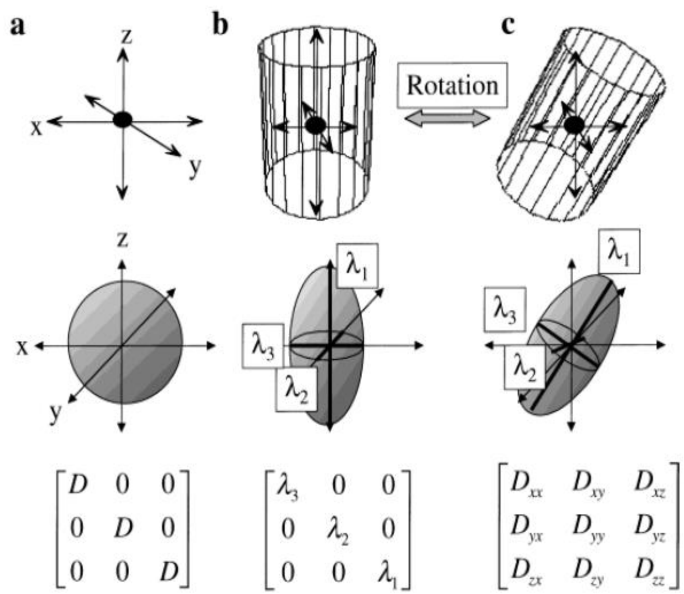


$D_{||} = 1.2 \times 10^{-3}\ mm^2/s$
$D_{\perp} = 0.4 \times 10^{-3}\ mm^2/s$

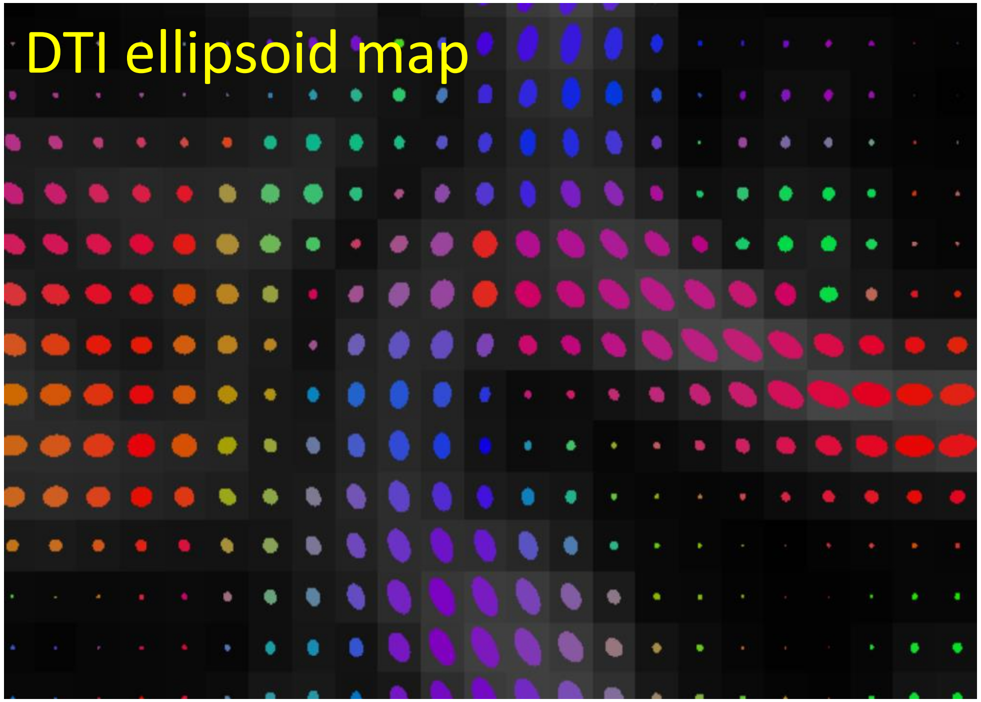
- Douek *et al.*, *JCAT* 1991

Diffusion Tensor MRI (DTI)

- A widely used diffusion MRI approach to map the fiber orientations and white matter integrity (*Basser et al., Biophys J 1994*)

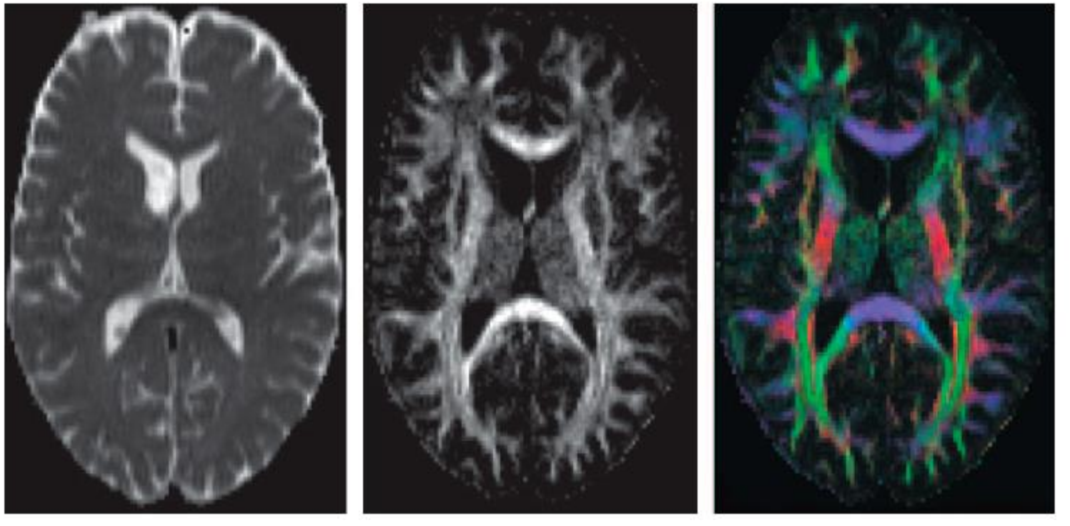


DTI models the intravoxel fibers as a diffusion ellipsoid



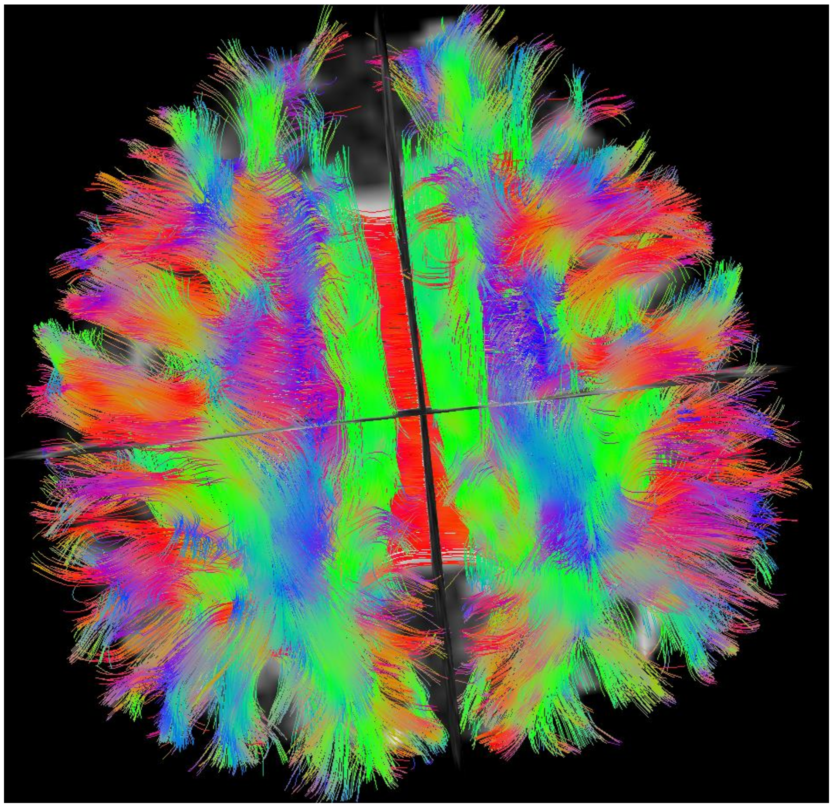
DTI quantitative indices

- These measures can represent the white matter integrity

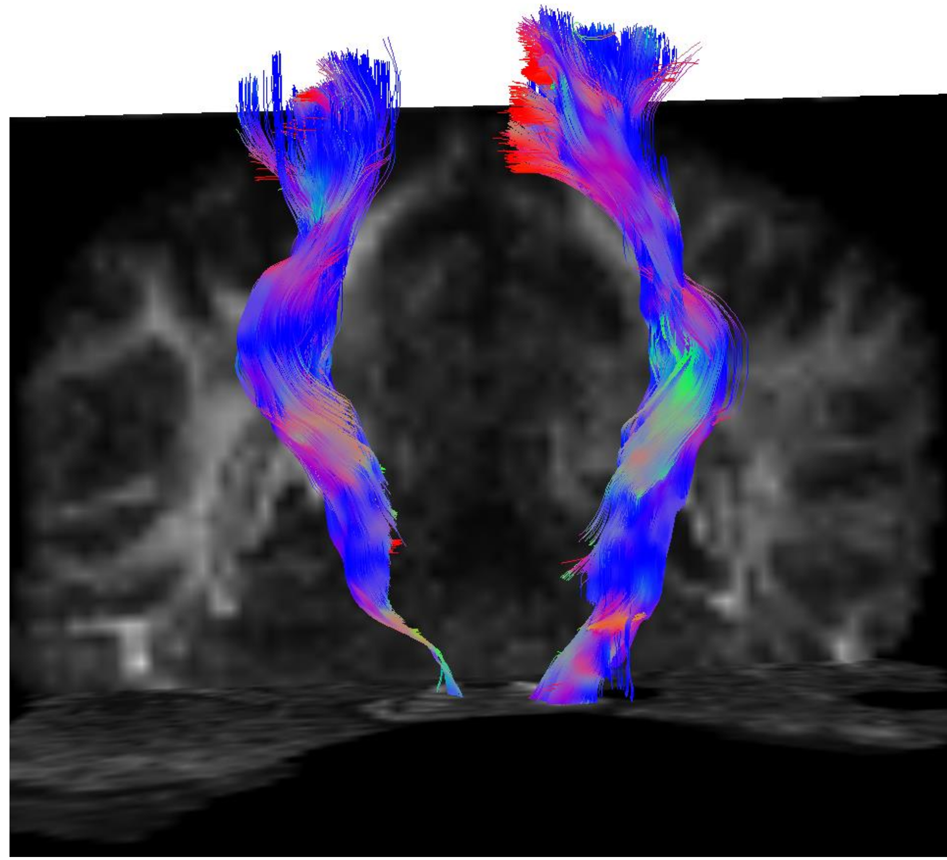


- Hagmann *et al.*, *RadioGraphics* 2006

Diffusion MRI Fiber Tracking



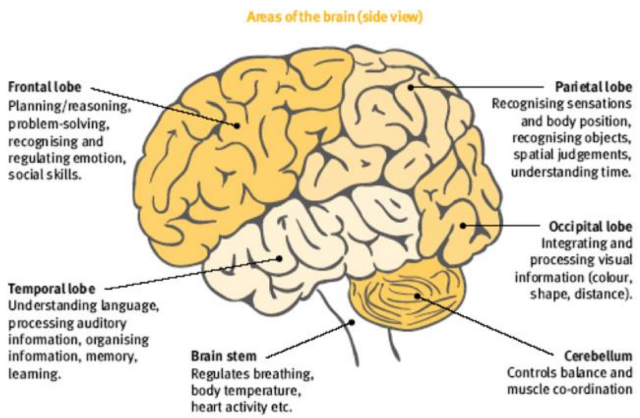
Whole Brain Tracts

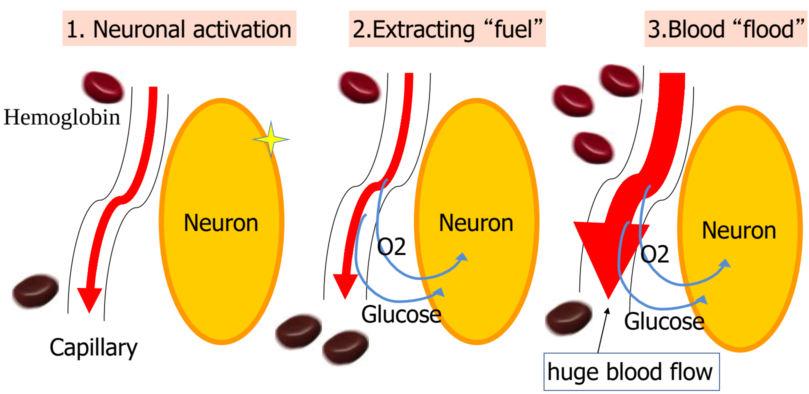


Corticospinal Tract

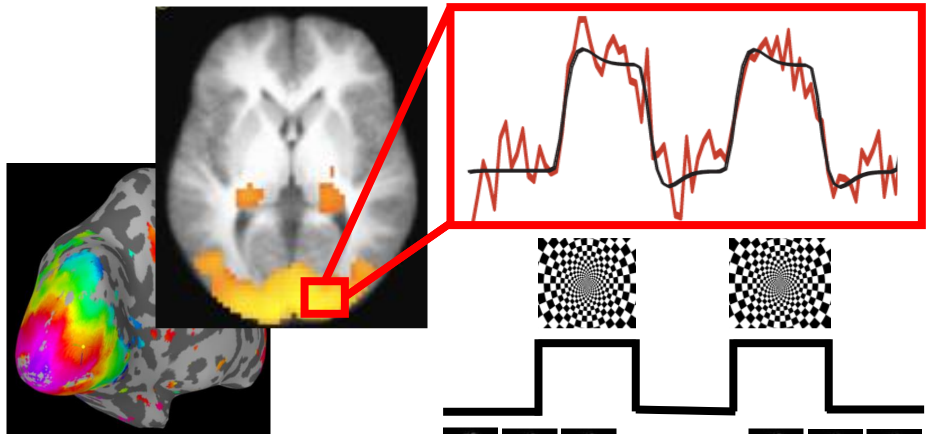
How do we measure the functional connectivity?

BOLD Functional MRI



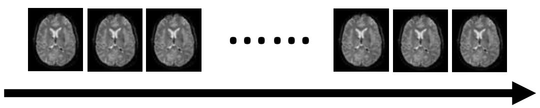


Task-based fMRI

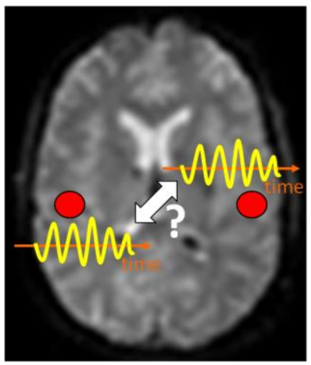


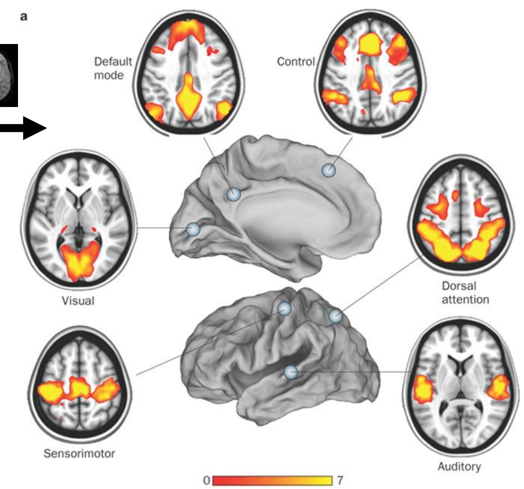
e.g. Visual fMRI

Resting-state fMRI



- No functional stimulus





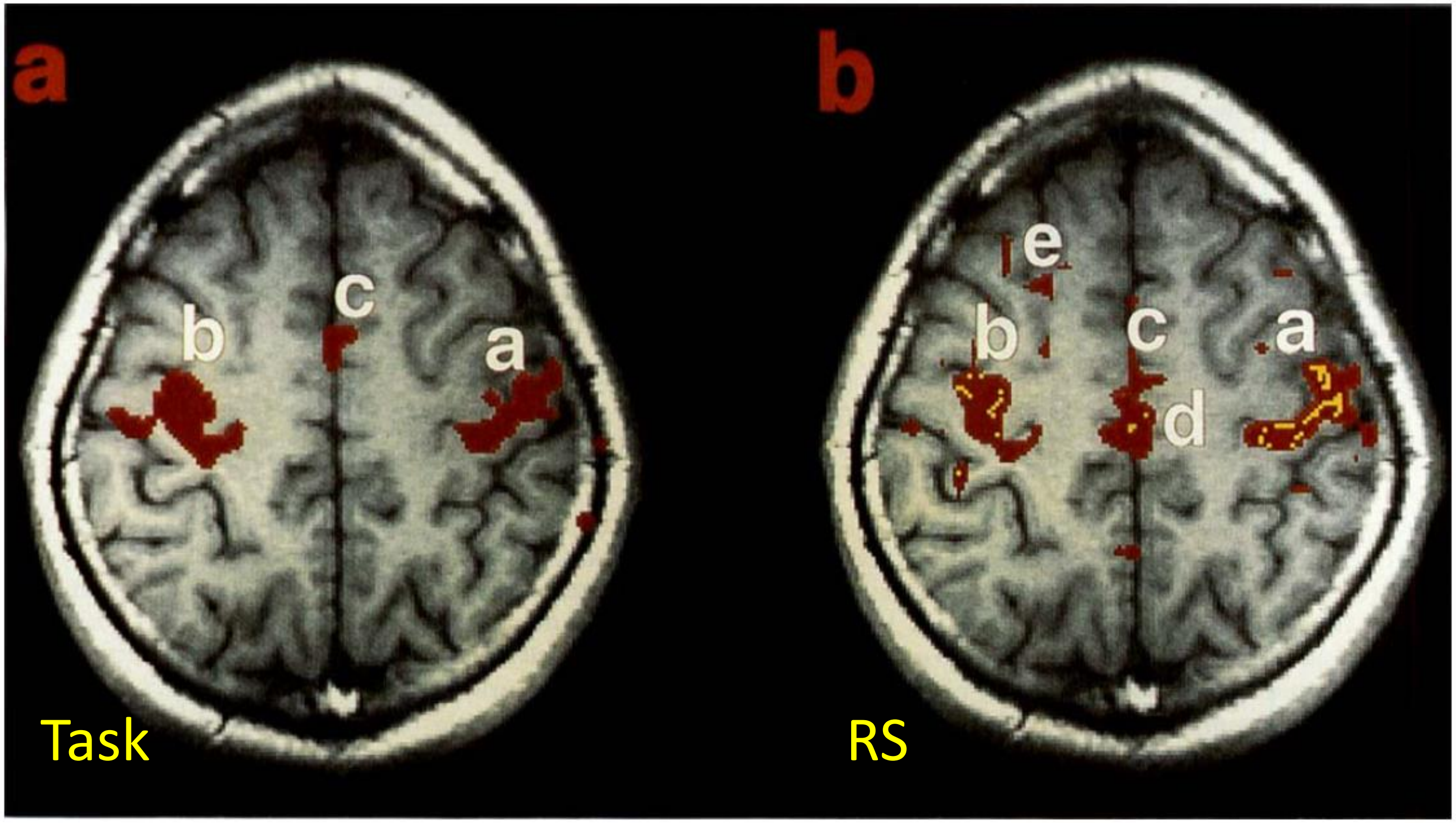
- Zhang and Raichle, Nat. Rev. Neuro., 2010

- fMRI: functional MRI

- BOLD contrast: blood-oxygenation-level-dependent contrast

Resting-state fMRI: first evidence

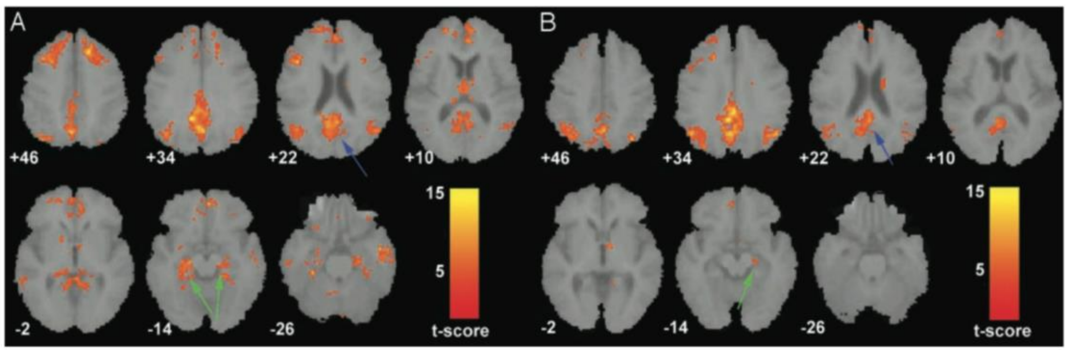
RS-fMRI: not just noise



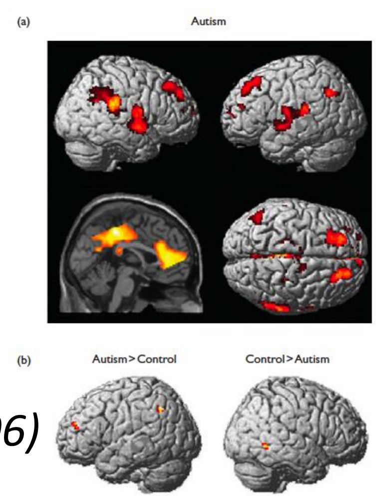
- Biswal et al., MRM 1995

Clinical applications with RS-fMRI

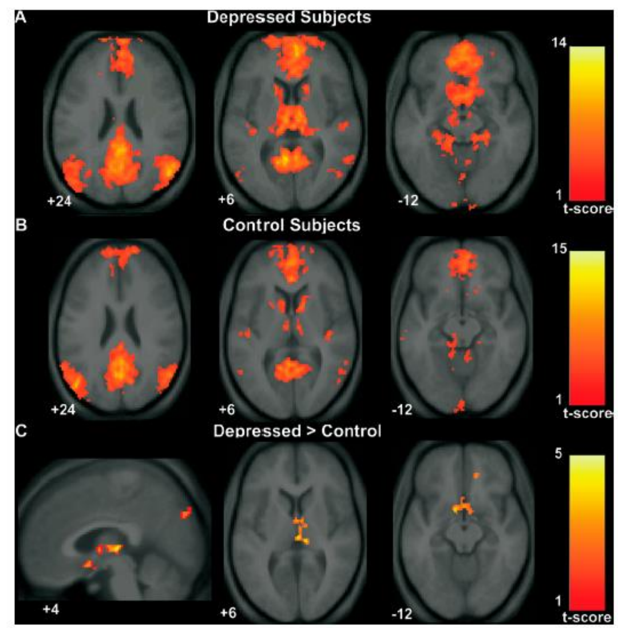
The resting human brain:
represents 2% of total body mass but consumes 20% of the body's energy



Healthy Elderly vs. Alzheimer's Disease (AD)
(Greicius et al., PNAS 2004)



Healthy control vs. Autism
(Cherkassky et al., NeuroReport 2006)



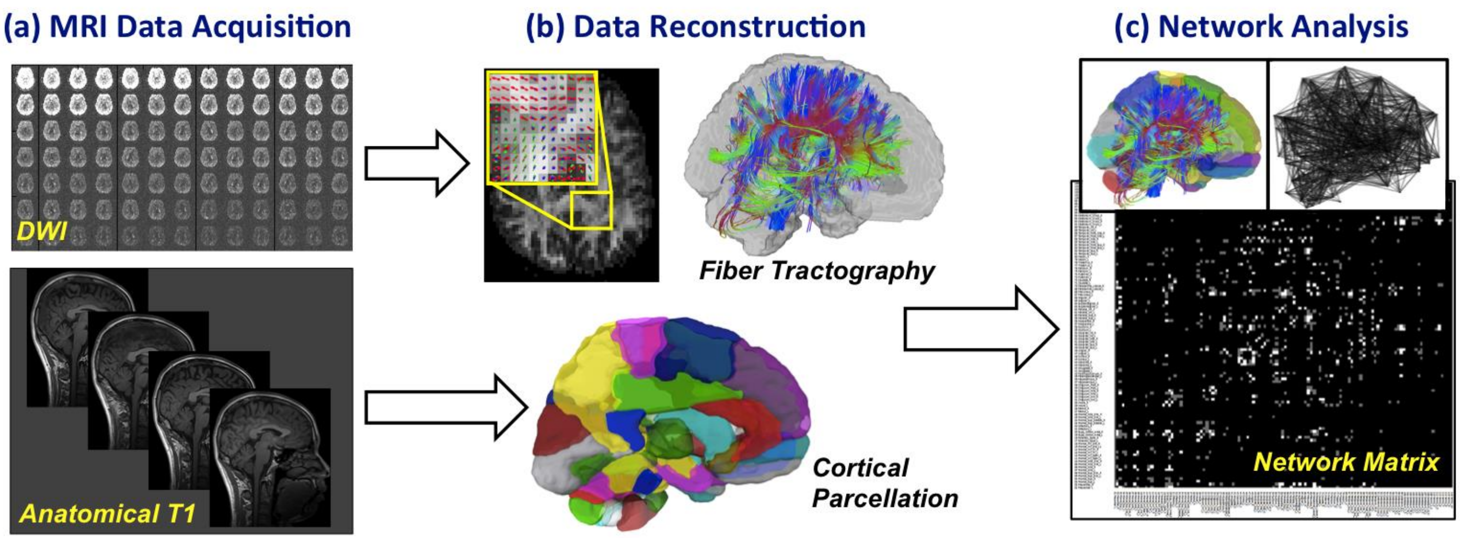
Healthy control vs. Depression
(Greicius et al., Biol Psychiatry 2007)

Computational approaches.

Now we have nodes and edges.

How to analyze the brain network with <u>graph theory</u>?

Graph Theoretical Analysis of a Brain Network



Define “**Connectivity**” between different cortical regions

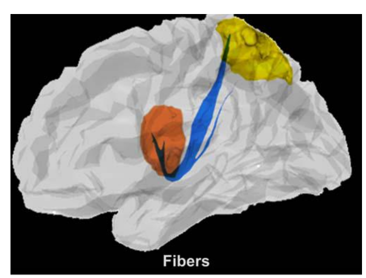
-***Fiber numbers***

-***Fiber density***

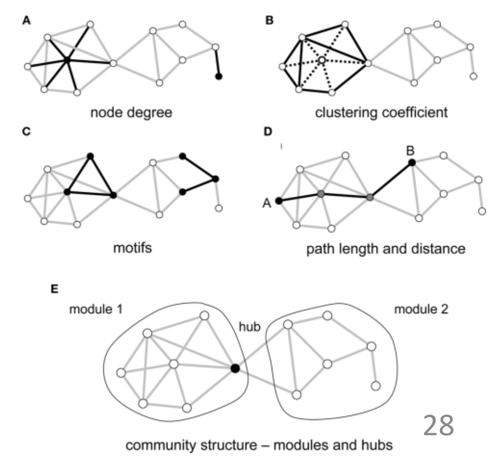
-***Fiber length***

-***Anisotropy***

-***Diffusivity***



Derive network properties with graph theory analysis



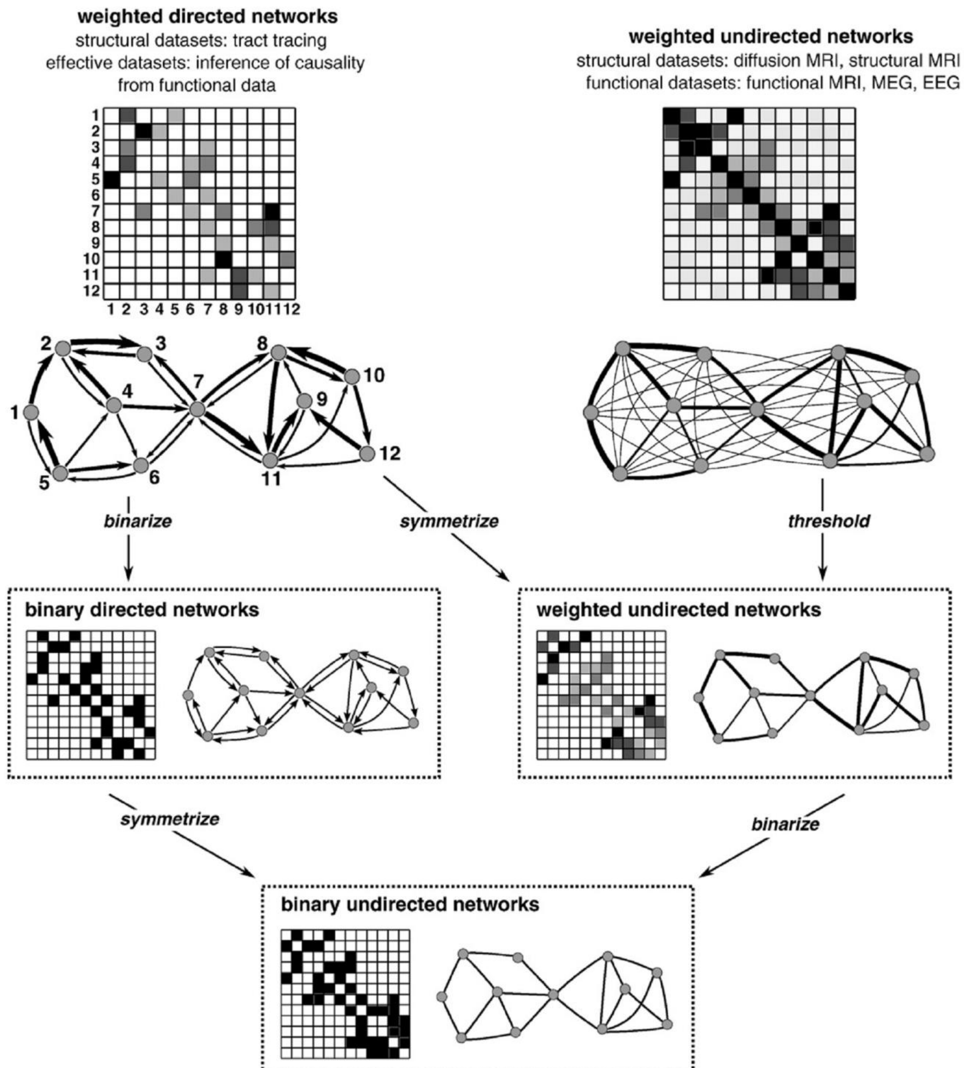
- Cho et al., JNSNE 2013

Characteristics of a network

Weighted vs. Unweighted

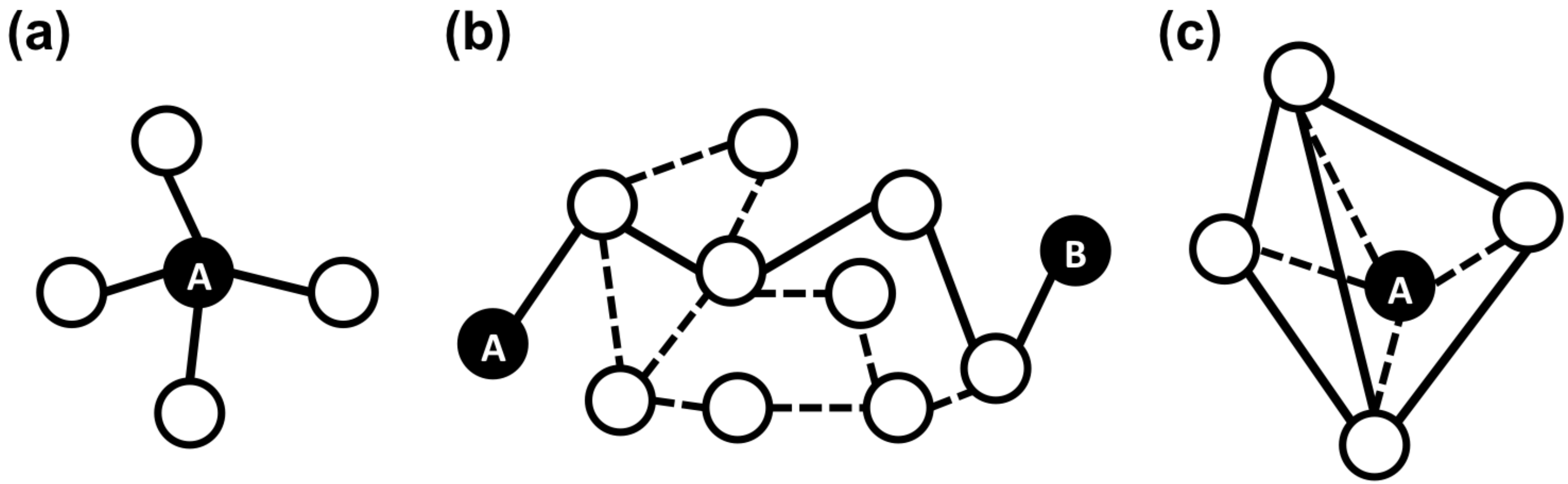
Directed vs. Undirected

Binarized



- Rubinov and Sporns, NeuroImage 52 (2010) 1059

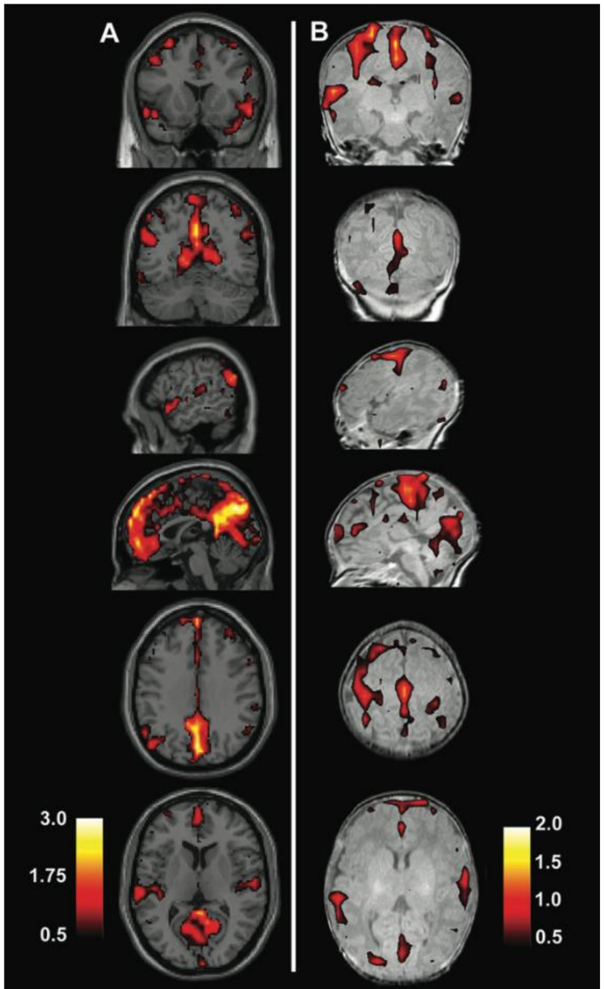
Some simple network measures



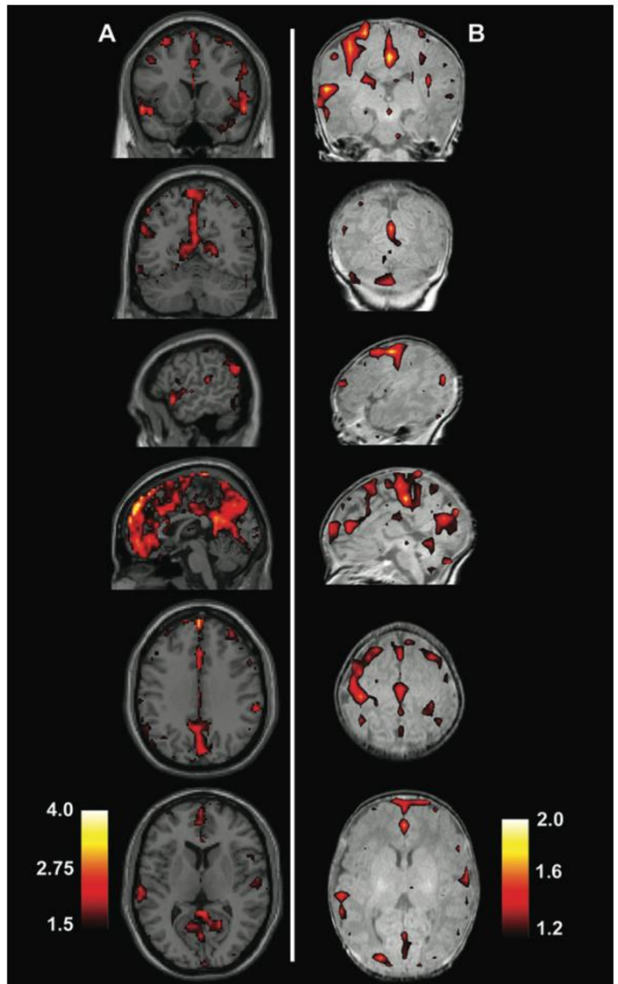
(a) Degree: the degree of node A is 4
(b) Shortest path length: the shortest path length between A and B is 5
(c) Clustering coefficient: the clustering coefficient of node A is 5/6 ([# of connections / # of max connections] between all neighbor nodes)

Brain Network in development

DEGREE Centrality



BETWEENNESS Centrality

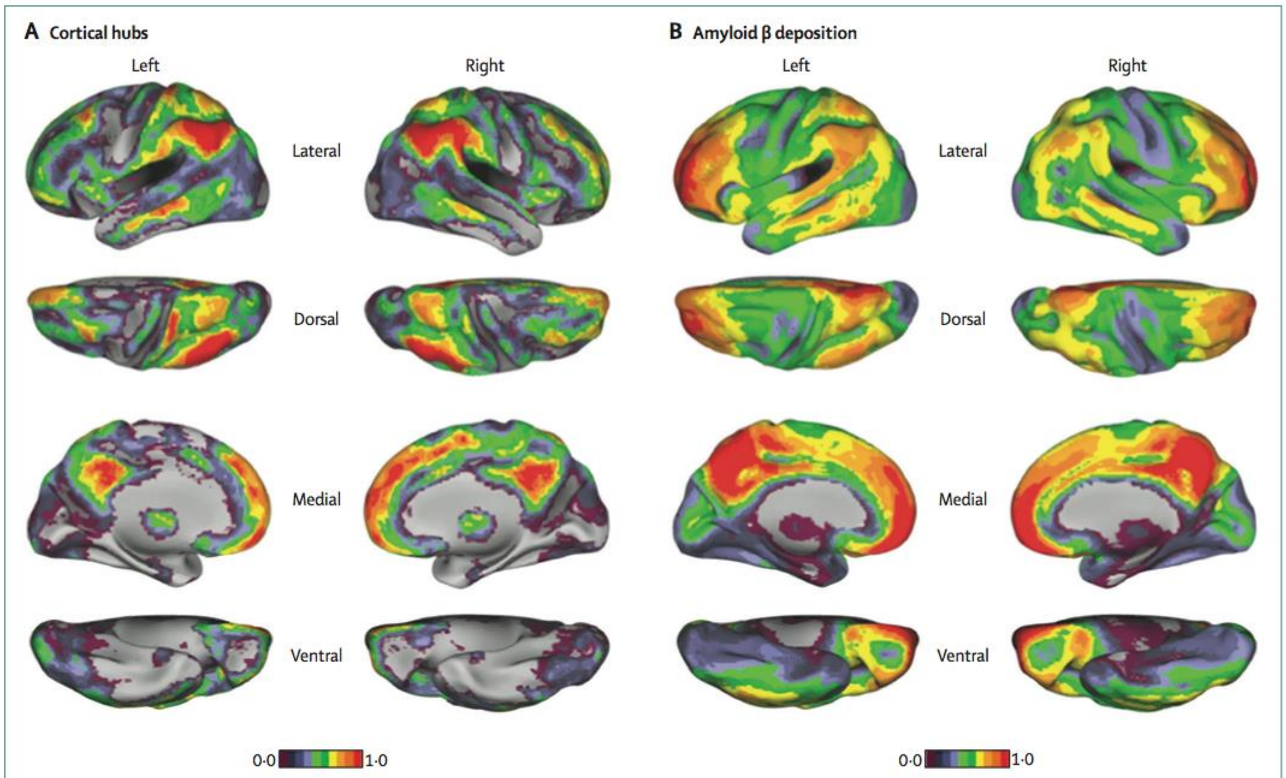


To investigate infants' brain network using resting-state fMRI, the results show the centrality is higher in primary cortex regions to support early development

- Fransson et al., Cerebral Cortex 2011

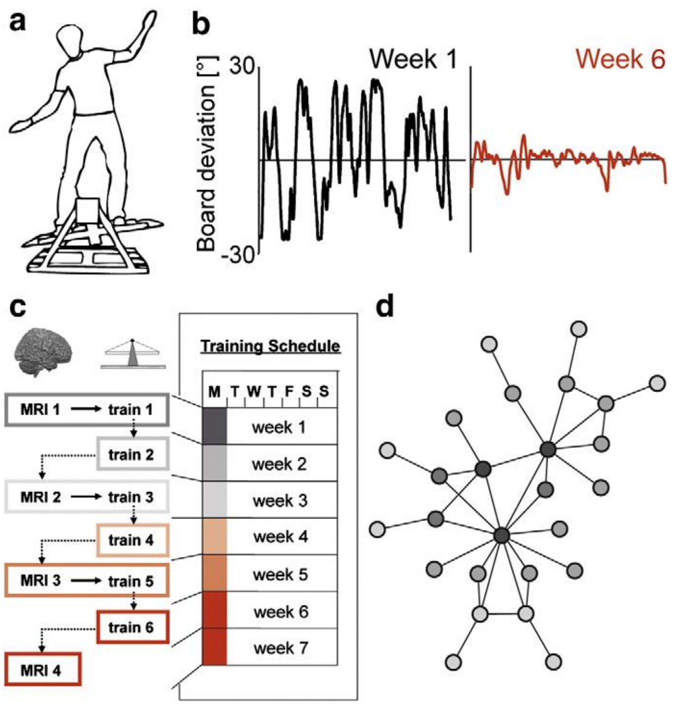
Network Centrality vs. Aβ deposition

The mappings of network centrality and Aβ deposition show a similar pattern in several areas including posterior cingulate cortex, precuneus, inferior parietal lobe and medial frontal cortex

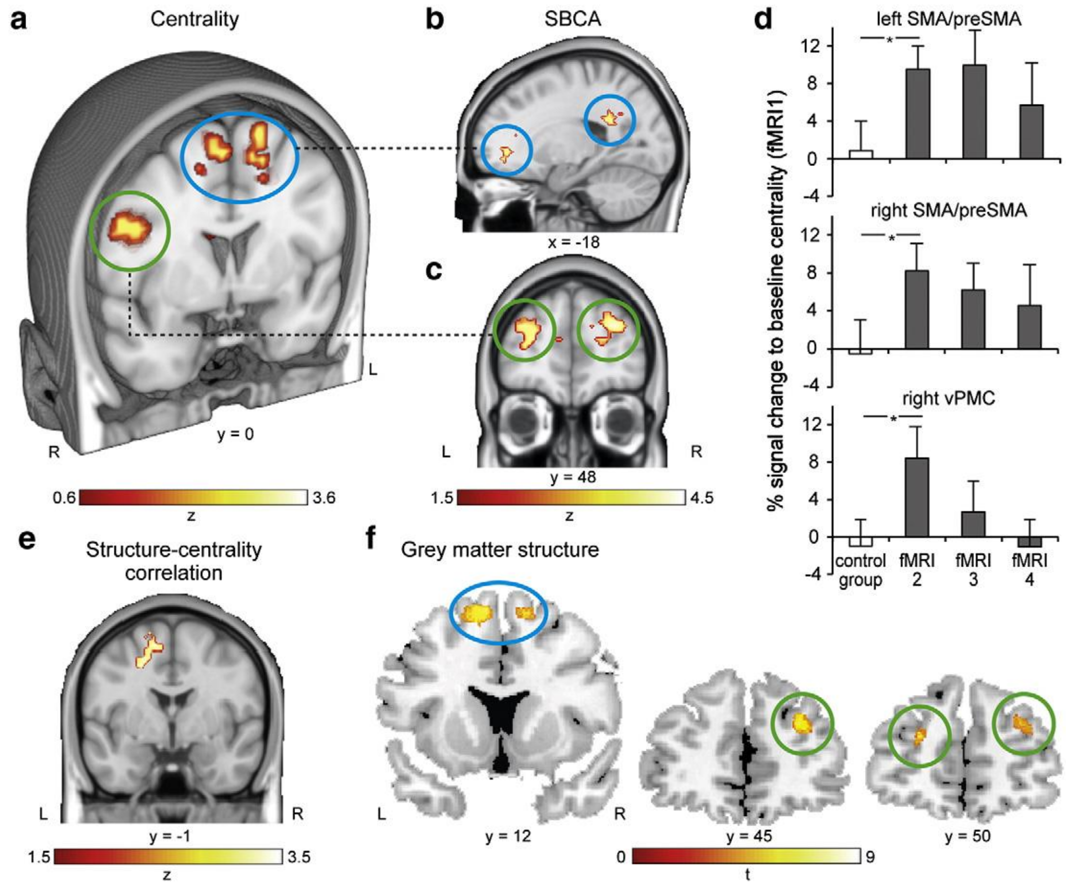


- Buckner et al., J neurosci, 2009

Training vs. Brain Network



Training experiments



Increase of Network Centrality

bilateral supplementary/pre-supplementary motor and right ventral premotor areas

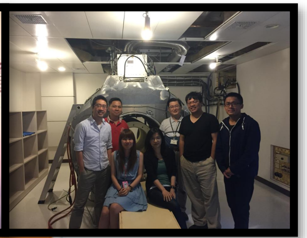
- Taubert et al., Neuroimage 2011

Application Example:
Brain Network Analysis using Graph Theory on Dementia

Preface

- Patients suffering from Alzheimer's disease (AD) are often diagnosed after progressively altered behavior, which are difficult to distinguish from the symptoms of mild cognitive impairment (MCI).
- **Neuroimaging approaches** provides anatomical, functional and metabolic information non-invasively and have been considered as promising tools to improve the diagnosis of AD.
- Brain network analysis utilizing graph theory could be potentially helpful to distinguish AD from MCI or even early aging. A joint development with machine learning approach for classification is also emergently needed.

Dementia research team at NHRI



Dr. Chih-Cheng Hsu
Epidemiological cohort strategy

Drs. Jen-Kun Chen and Li-Wei Kuo
PET/MR multimodality imaging markers strategy

Develop an integrated biomarker platform for early diagnosis of Alzheimer's disease

Drs. Yu-Li Liu and Yun Wang
Eotaxin-relating pathway strategy

Dr. Jyh-Lyh Juang
miRNAs involved in *Eotaxin* expression or T cell activation strategy

Materials and Methods

➢ Patient recruitment

- All the clinical assessments and experiments were performed in Dalin Tzu-Chi Hospital. A total of **71** subjects were recruited in MR study, including **26** healthy control subjects (HC), **22** MCI and **23** AD.

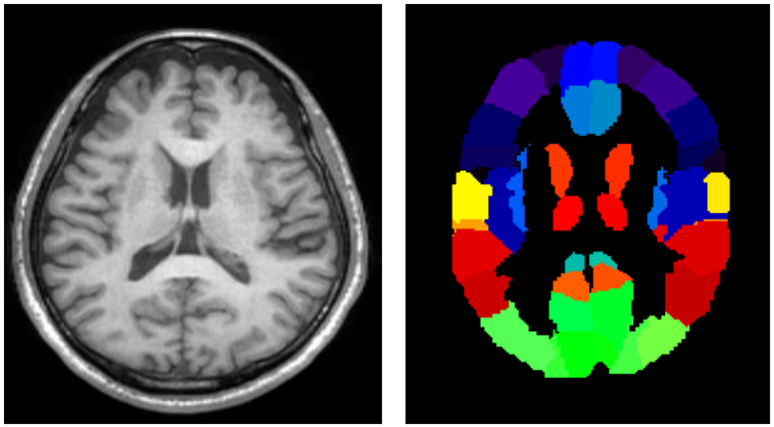
➢ MR experiments

- All MR experiments were performed on a 1.5T MRI scanner (HDxt, GE, USA). For brain functional network, we acquired 3D T1-weigthed images and resting-state functional MRI data. For structural network, we acquired DTI data with 30 gradient directions (b = 1000 s/mm^2).

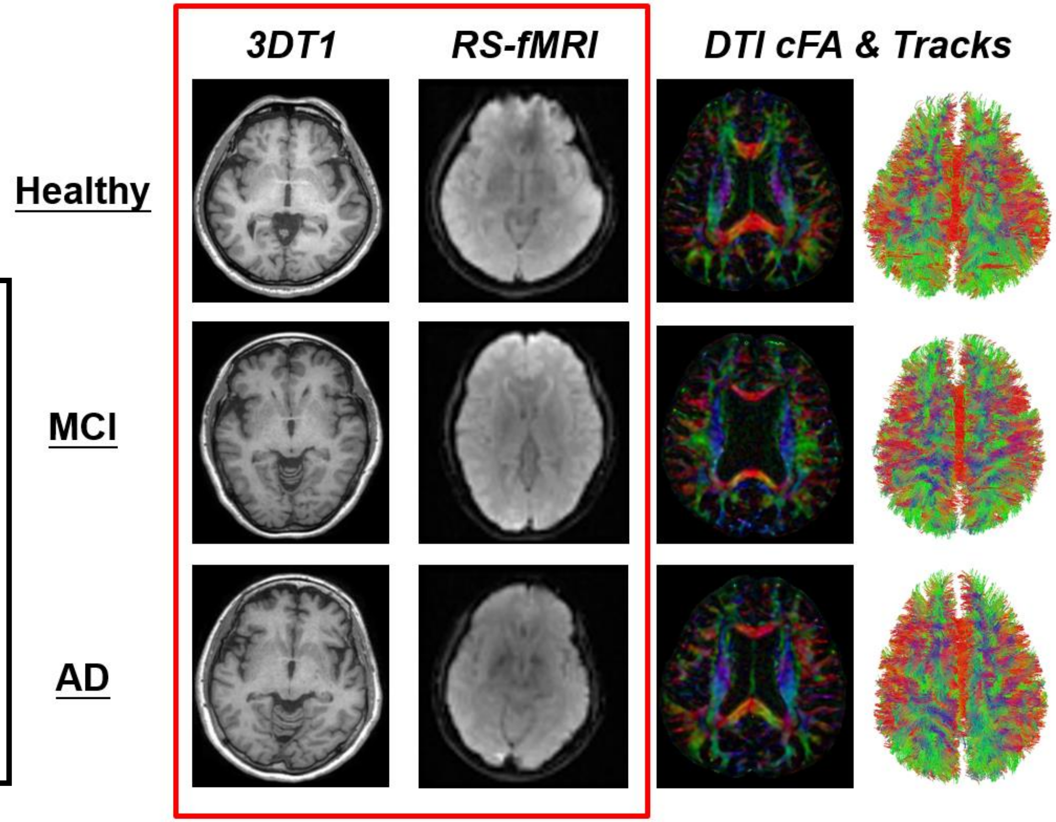
➢ Analysis approaches

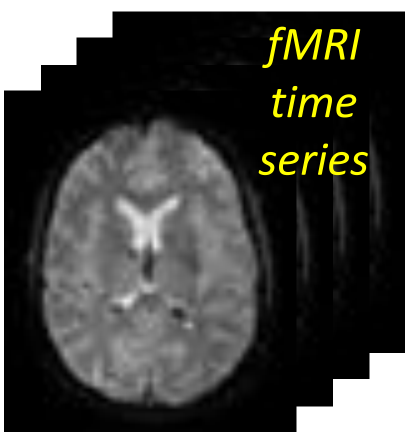
- In this study, we incorporated both statistical and machine-learning approaches on brain network measures to investigate the functional alterations of brain in AD and aimed to establish a useful framework for classifying HC, MCI and AD.

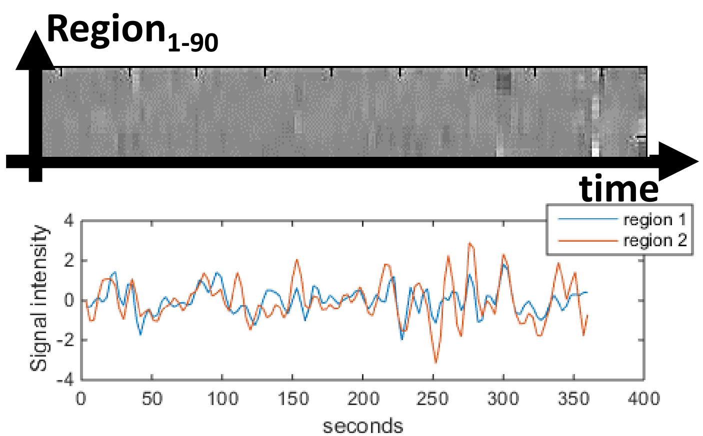
Brain Functional Network Analysis



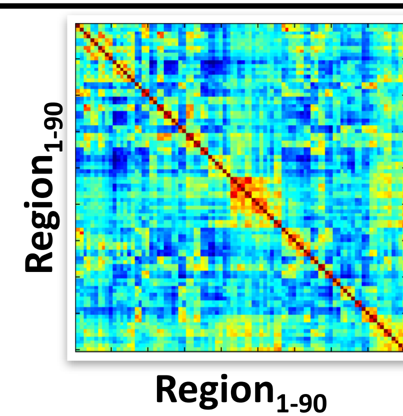
How to define NODE from MRI







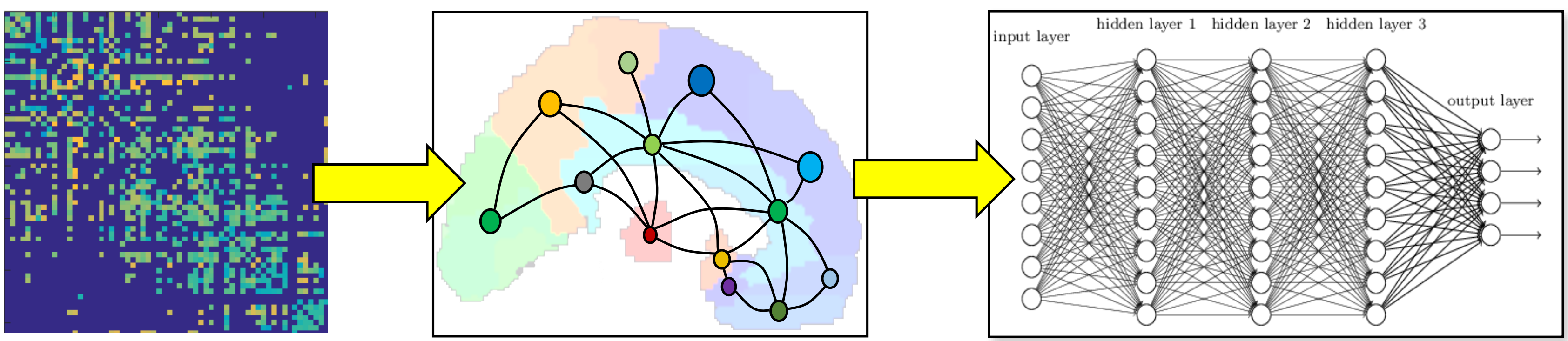
Functional connectivity calculation



Functional network matrix

Build a deep neural network model

- In this work, we aimed to establish a classification model based on brain network analysis and deep neural network
- The classification accuracies using different types of functional connectivity were compared



Connectivity **Network Analysis** **Deep Neural Network**

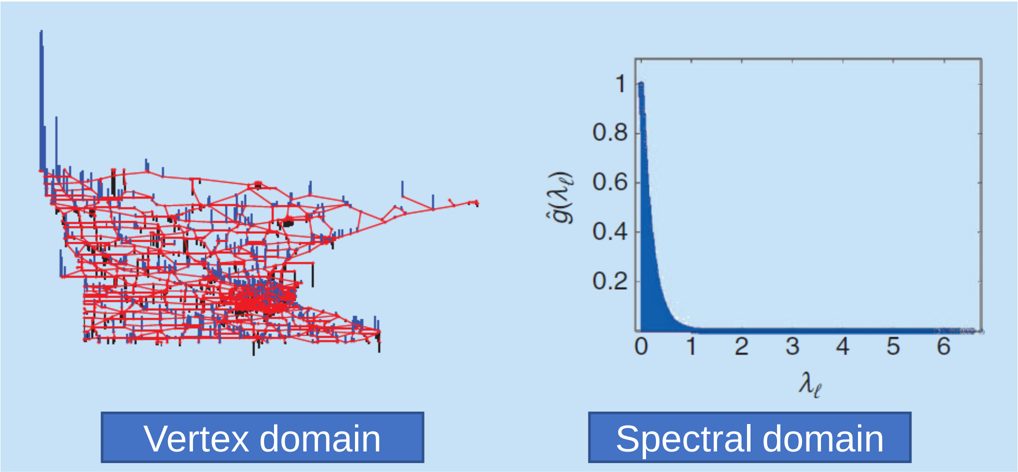
Comparison of functional connectivity on classification accuracy

- Normalized fMRI time series (across 90 AAL regions) was used for functional connectivity calculation
    - **Pearson’s correlation, covariance, normalized mutual information (NMI) and GSP graph learning**
- Connectivity matrix sparsification
    - **For Pearson’s, covariance and NMI, the sparsification range is [0.1 0.3]**
    - **For GSP, no sparsification is needed**
- Four kinds of network measures were used as features in training model
    - **Nodal degree, clustering coefficient, local efficiency, pagerank centrality**

Graph Signal Representations in Spectral Domains

- The Graph Fourier Transform can be defined on the vertices of a graph and represent graph signals on spectral domain

$$\hat{f}(\lambda_\ell) := \langle \mathbf{f}, \mathbf{u}_\ell \rangle = \sum_{i=1}^{N} f(i) u_\ell^*(i). \qquad f(i) = \sum_{\ell=0}^{N-1} \hat{f}(\lambda_\ell) u_\ell(i).$$

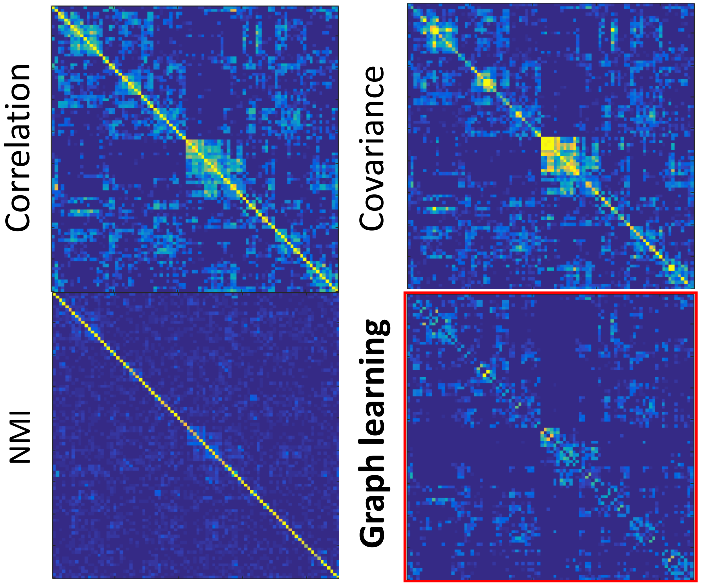


A graph on vertex domain and its corresponding spectrum domain (Shuman et al., 2013)

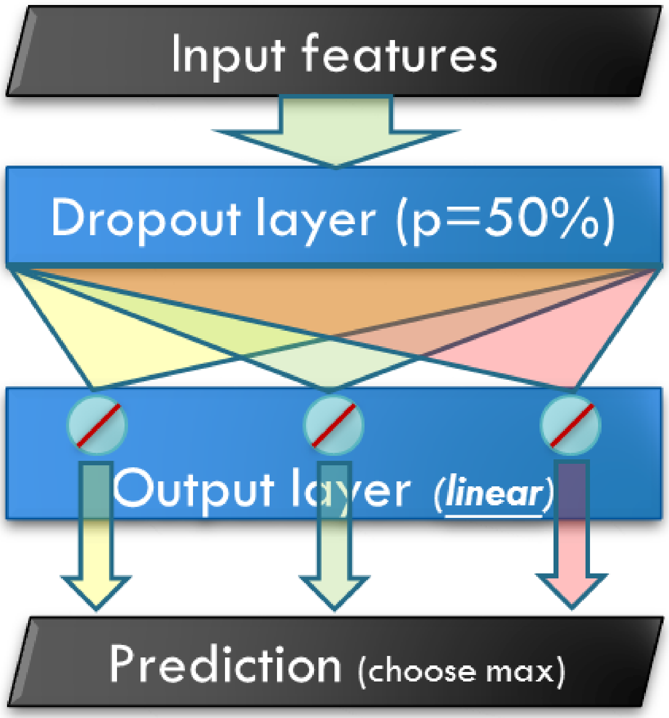
Graph Signal Processing

- **Relationship between eigenvectors and frequency**
  - Eigenvectors associated with small eigenvalues indicate the signals vary slowly across the graph
  - Eigenvectors associated with large eigenvalues indicate the signals oscillate rapidly and are more likely to have dissimilar values on adjacent vertices

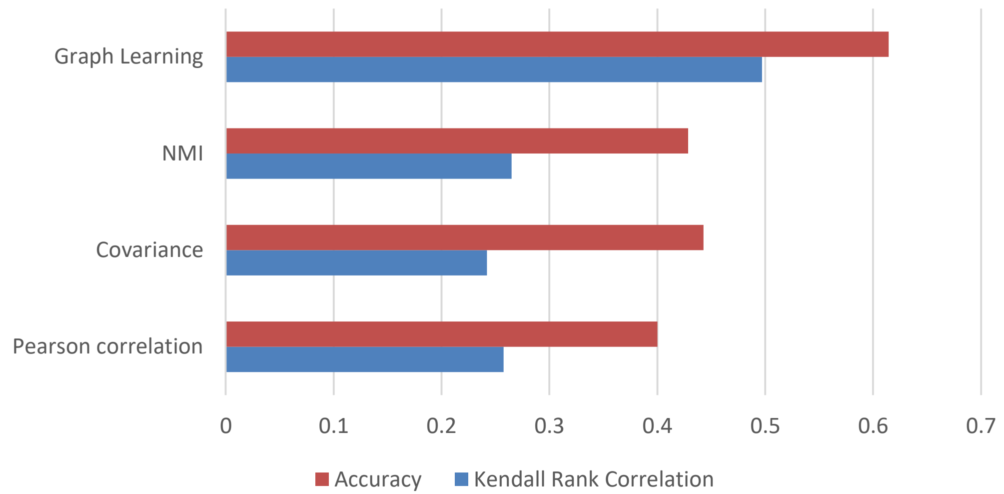
In our work, we utilize graph learning technique (Kalofolias et al., AISTATS 2016) to process the functional connectivity matrix by maximizing smoothness of signals on the graph



Classification of HC/MCI/AD using deep neural network



Architecture of the Classifier Implemented using TensorFlow



Connectivity	Pearson corr.	Covariance	NMI	Graph learning
Accuracy	0.4	0.44	0.43	0.61

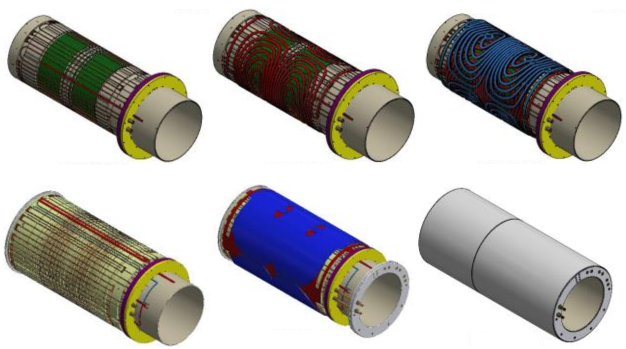
Google's TensorFlow™

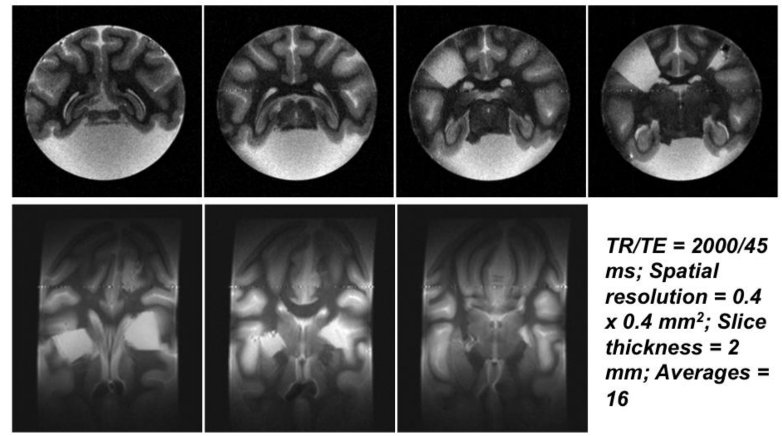
- Lin et al., ISMRM'17

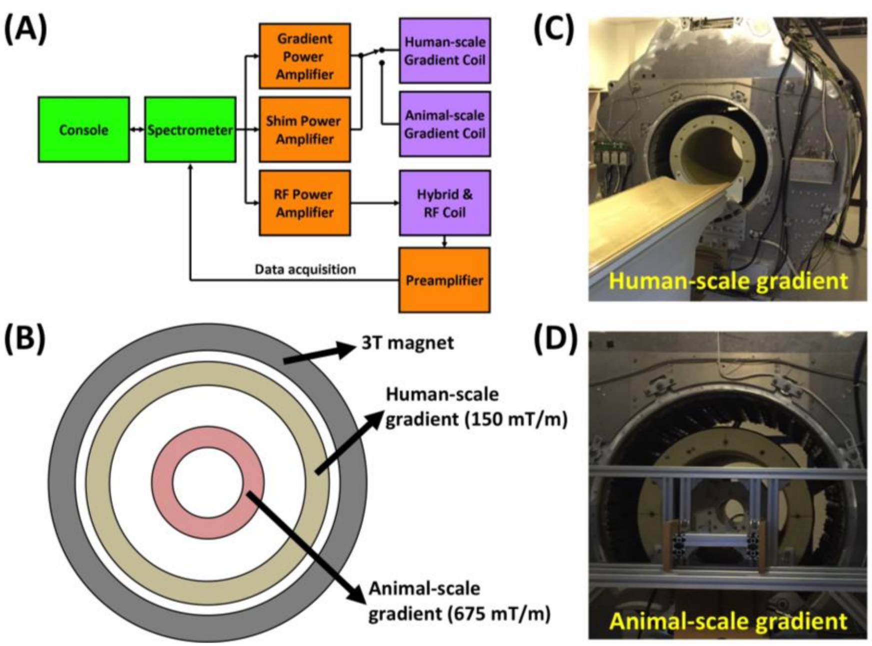
Summary

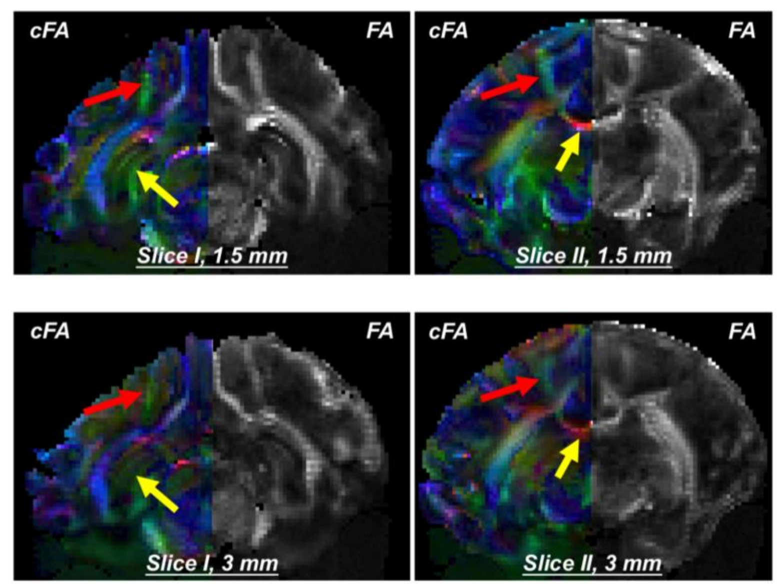
- The AI has significantly changed the development of medical imaging instrumentations during the past few years. More coming in future!
  - ✓ ***Although potentially useful, its reliability and validity on clinical use still needs further investigation***
- Graph theoretical analysis could be potentially useful in identifying altered network topologies of brain structures and functions
  - ✓ ***A joint development with deep learning is highly expected***
- **”Data” is the “key”**: to enhance the data quality by building a ***high-performance dedicated brain MRI***

A high-performance dedicated brain 3T MRI at NHRI

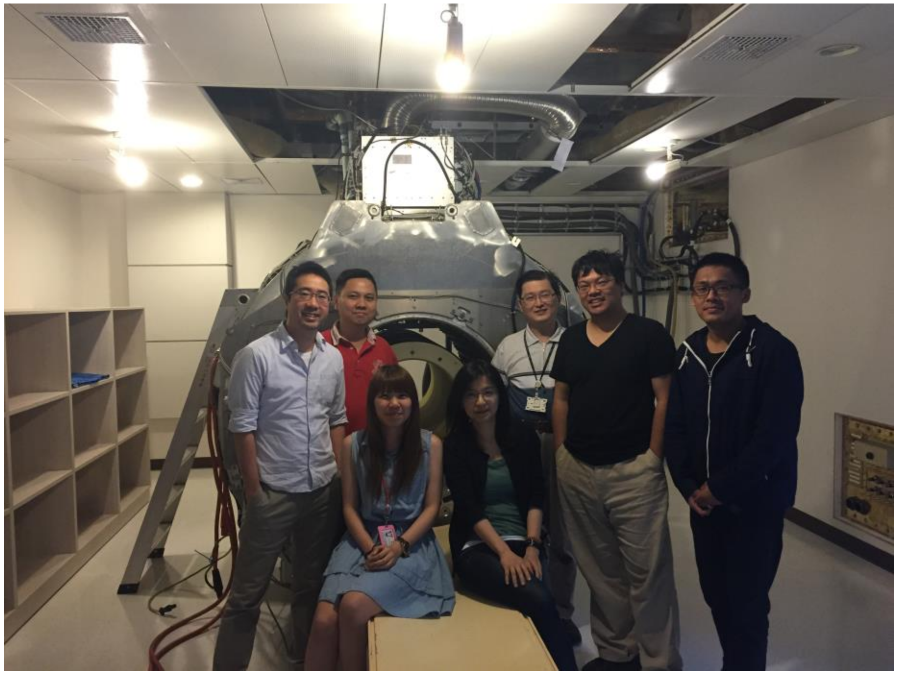








Acknowledgements



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