Brain network topological changes in neuropsychiatric disorders: from voxels to networks

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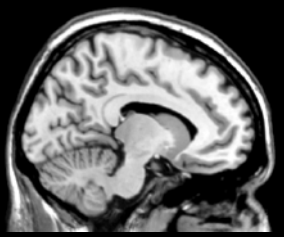
Meeting the Statistical Challenges in High Dimensional Data and Complex Networks

Institute of Mathematical Sciences, National University of Singapore
February 14th, 2018

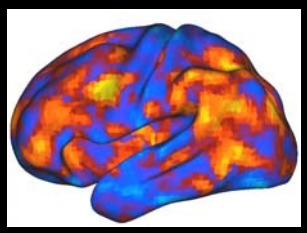
DukeNUS Medical School

MULTIMODAL NEUROIMAGING LABORATORY

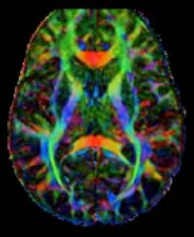
Multimodal network-sensitive in-vivo MR imaging methods



Grey matter volume (MRI)

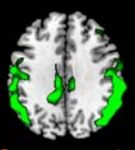


BOLD signal (Task-free fMRI)

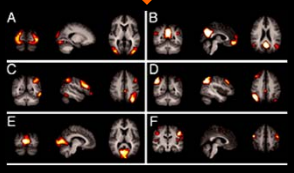


White matter microstructure (DTI)

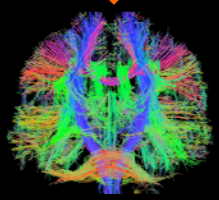
Atrophy



Structural covariance network



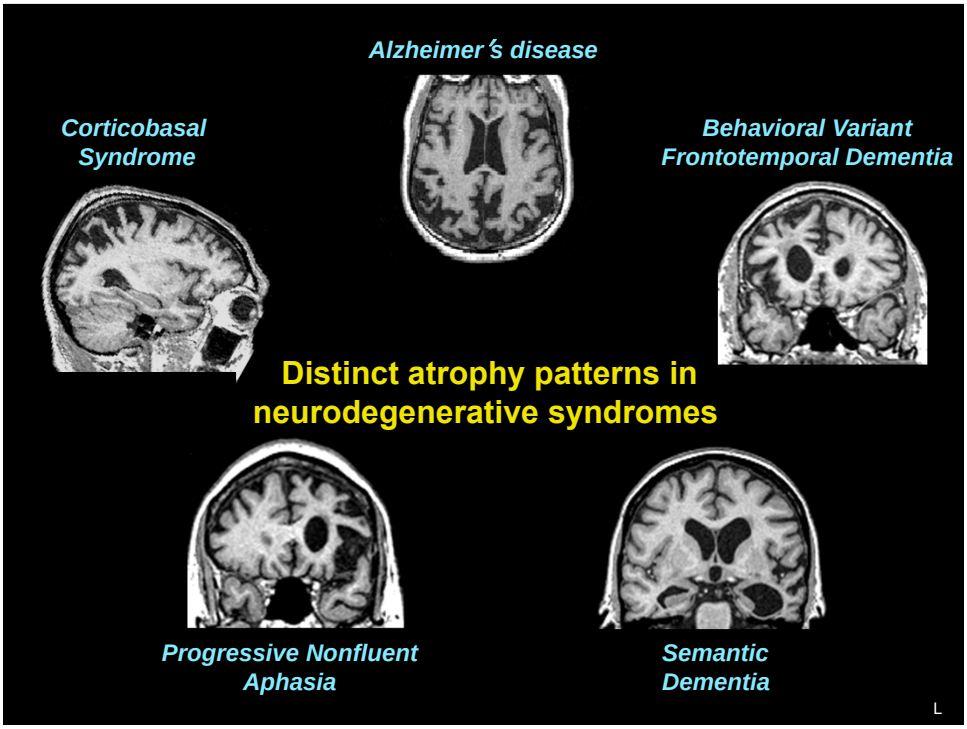
Intrinsic connectivity network (ICN)

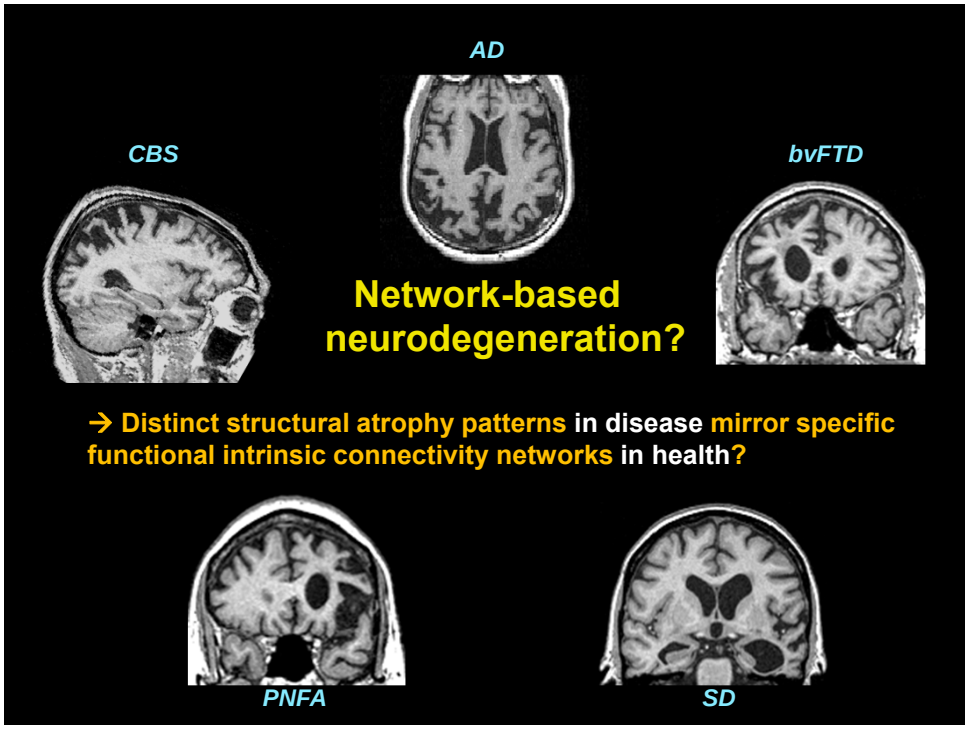


Structural connectivity

Outline

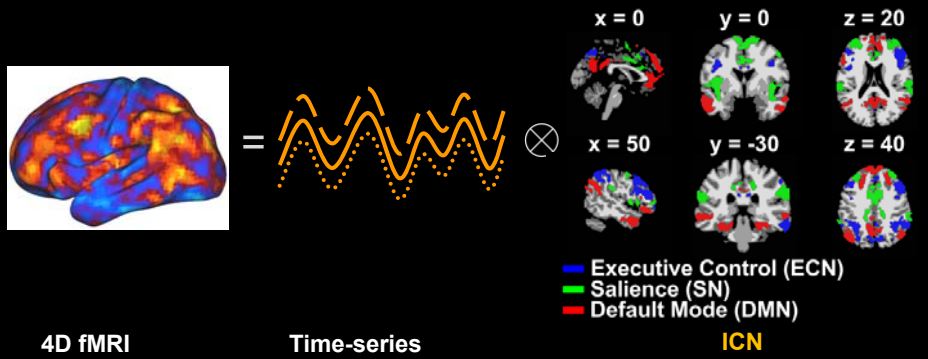
1. Network-based neurodegeneration using network-sensitive imaging
2. Detect symptoms-related changes and predict outcomes in neuropsychiatric disorders
3. Longitudinal functional network changes underlying cognitive decline in healthy ageing and the influence of APOE genotype
4. Spontaneous eyelid closure links vigilance fluctuations with dynamic connectivity states





Intrinsic connectivity networks

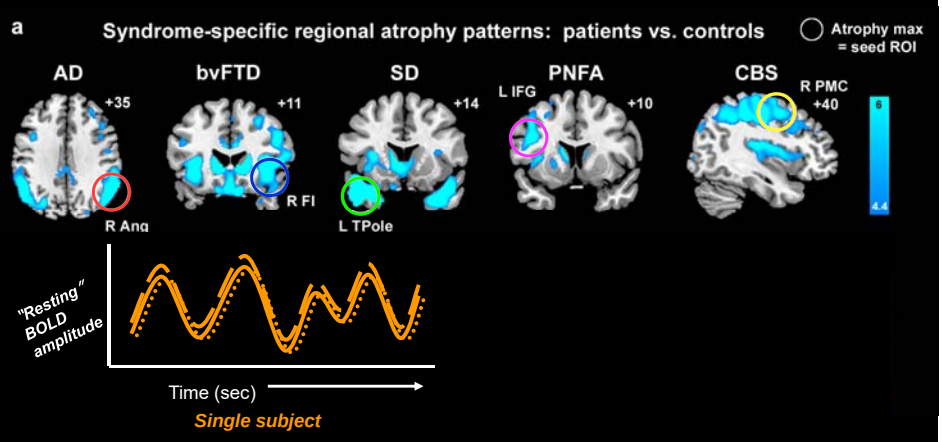
- fMRI: blood-oxygenation-level-dependent (BOLD) signal
- Intrinsic connectivity networks (ICNs) from task-free fMRI
  - Synchronization of spontaneous low frequency signal (<0.1Hz)



Video courtesy of Vincent

Biswal et al, 1995; Damoiseaux et al. PNAS 2006; Smith et al, PNAS 2009; Yeo et al, 2011

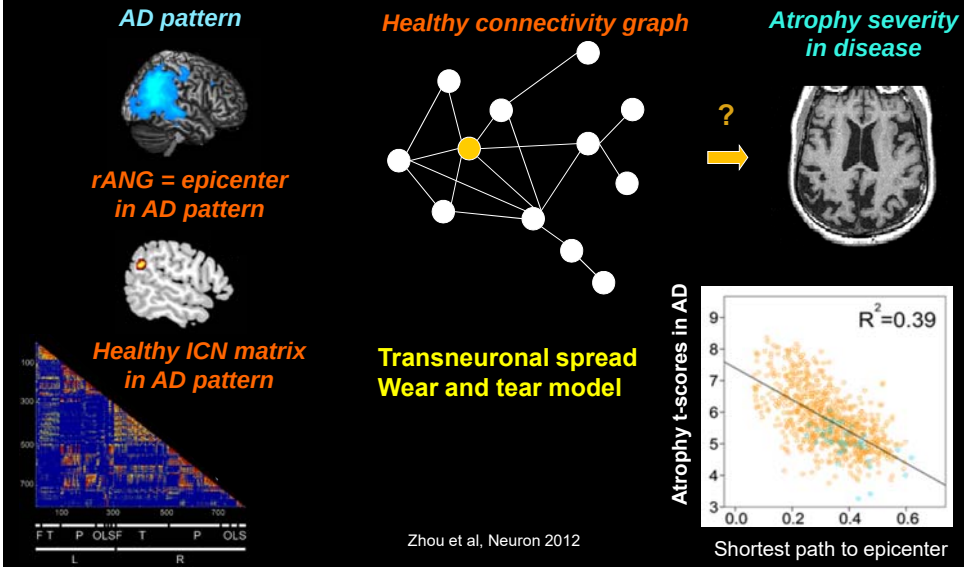
Syndrome-specific atrophy patterns mirror functional ICNs in healthy controls



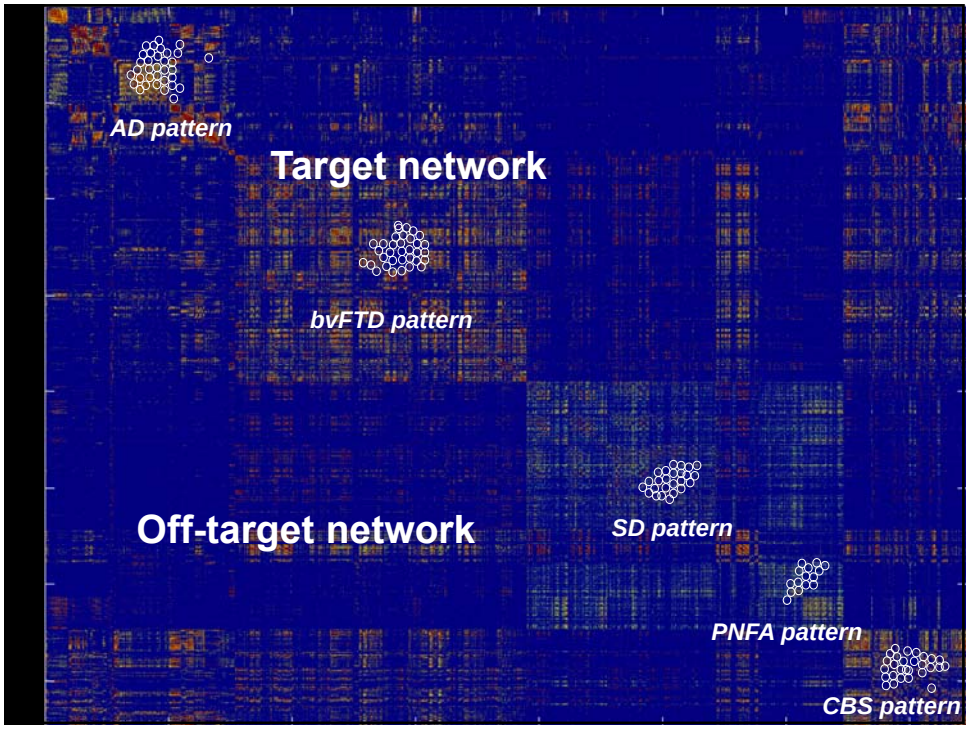
Seeley, Crawford & Zhou, Neuron 2009

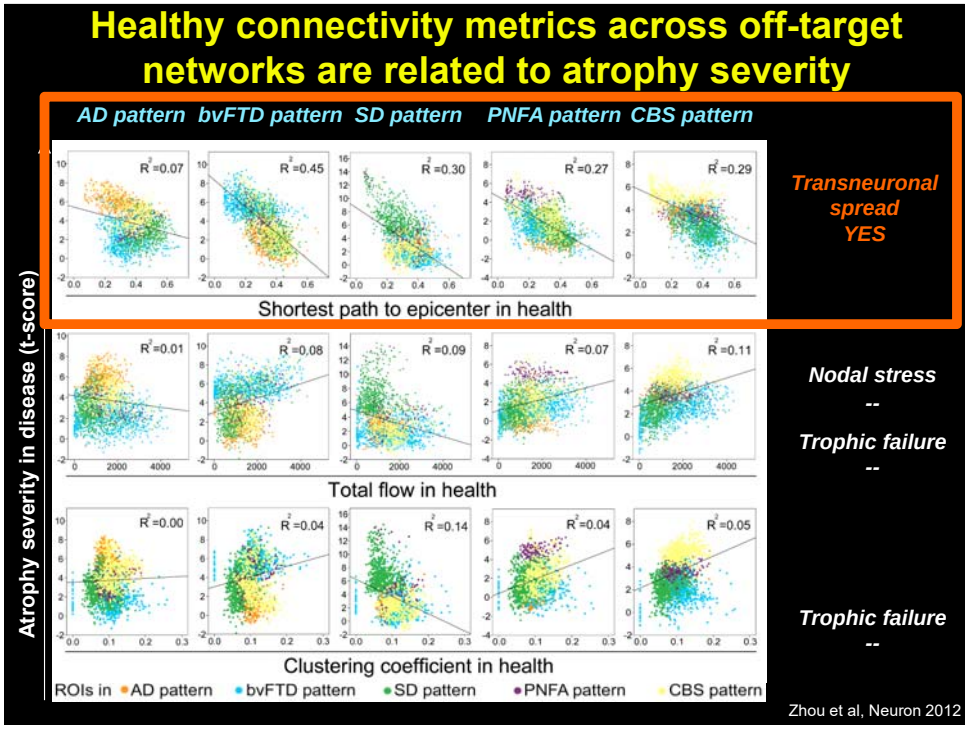
Predicting regional neurodegeneration from the healthy functional brain connectome

Can healthy connectivity give us insight into mechanisms of network breakdown?



Zhou et al, Neuron 2012


AD pattern
Target network
bvFTD pattern
Off-target network
SD pattern
PNFA pattern
CBS pattern


Healthy connectivity metrics across off-target networks are related to atrophy severity
AD pattern
bvFTD pattern
SD pattern
PNFA pattern
CBS pattern
Atrophy severity in disease (t-score)
R²=0.07
R²=0.45
R²=0.30
R²=0.27
R²=0.29
Shortest path to epicenter in health
Transneuronal spread YES
R²=0.01
R²=0.08
R²=0.09
R²=0.07
R²=0.11
Total flow in health
Nodal stress --
Trophic failure --
R²=0.00
R²=0.04
R²=0.14
R²=0.04
R²=0.05
Clustering coefficient in health
Trophic failure --
ROIs in AD pattern bvFTD pattern SD pattern PNFA pattern CBS pattern
Zhou et al, Neuron 2012

Outline

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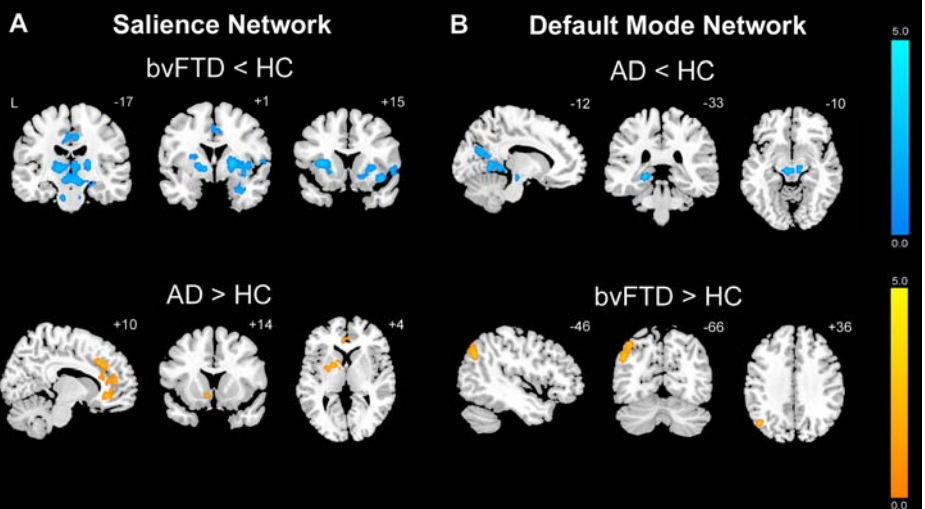
BvFTD and AD: Divergent functional connectivity changes in SN and DMN

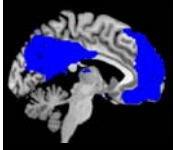


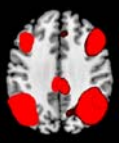
ICA approach

p < 0.05, height & extent corrected

Zhou et al, Brain 2010

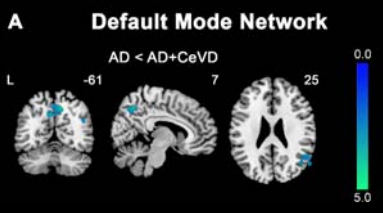
AD and AD+CeVD had divergent FC in the default-mode and executive control networks

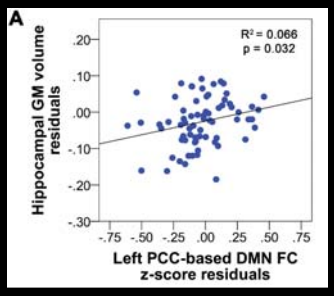




Chong et al, Brain 2017

AD and AD+CeVD: network degeneration phenotype





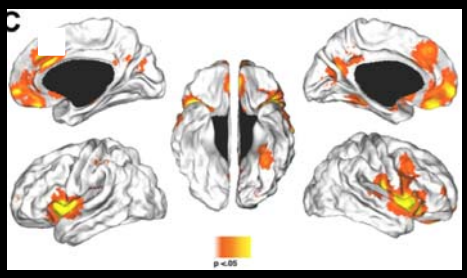
Chong et al, Brain 2017

ICN dysconnectivity in psychosis

Disrupted ICNs underlying the pathophysiology of schizophrenia

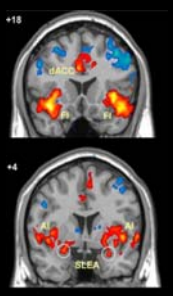
- Proximal salience dysfunction model
- Grey matter atrophy in the salience network
- Reduced insular functional connectivity in schizophrenia

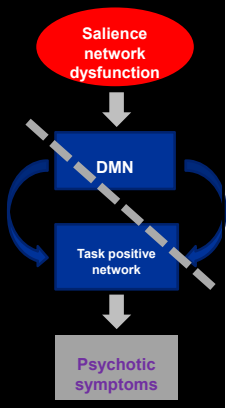
Q: Prodromal stage of schizophrenia?



Fornito et al. Schiz Research 2009
Palaniyappan et al. J Psy Neurosci 2012

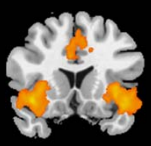
Salience Network

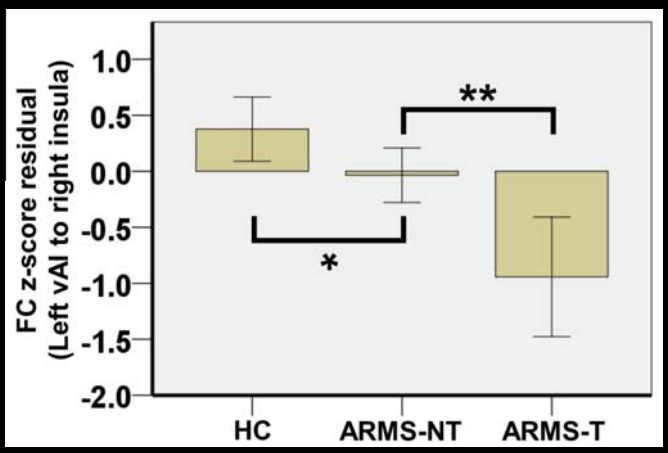




Klauser* and Zhou* et al, Schizo. Bulletin, 2015
Zhou and Seeley, Biological Psychiatry, 2014

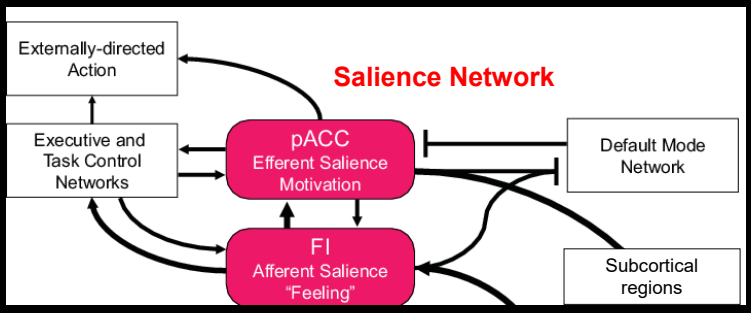
Baseline salience network functional connectivity predict transition to psychosis



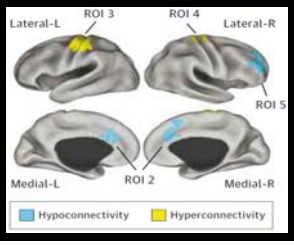


Wang et al, Psychological Medicine 2016

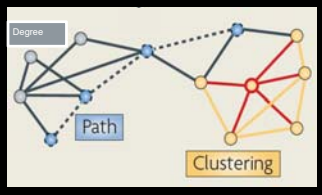
Beyond the salience network: Functional network topology → outcomes



ARMS-T vs ARMS-NT



Topological metrics

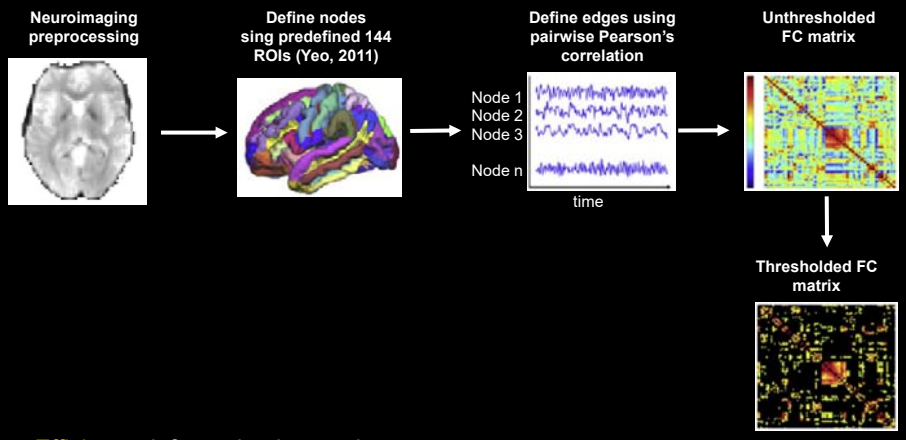


(Bullmore et al. Nat Rev Neurosci 2009)

Zhou & Seeley, Bio. Psychiatry, 2014; Palaniyappan et al, J. Psy. Neuro. 2012

Study design overview

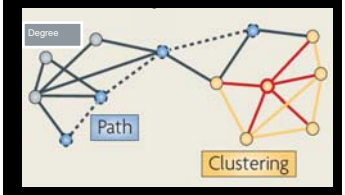
48 HC, 76 ARMS-NT, 12 ARMS-T from Phase 1 neuroimaging data from LYRIKS study



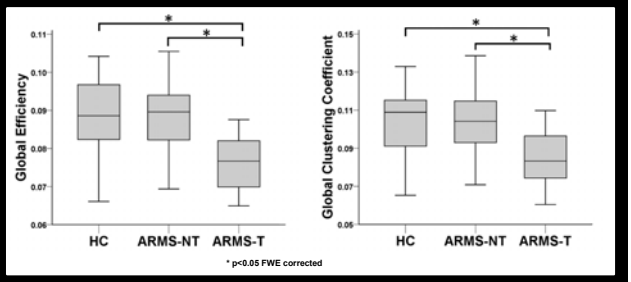
- Efficiency: information integration
- Clustering coefficient: network segregation
- Graph community: modularity

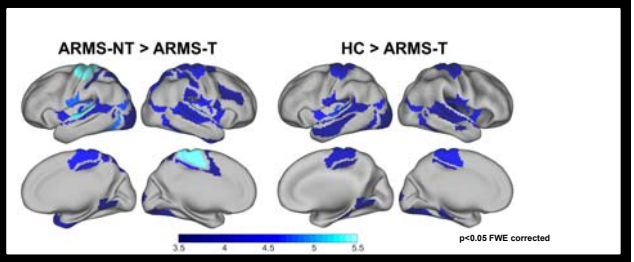
Reduced network efficiency at baseline in ARMS who transition to psychosis

Topological metrics



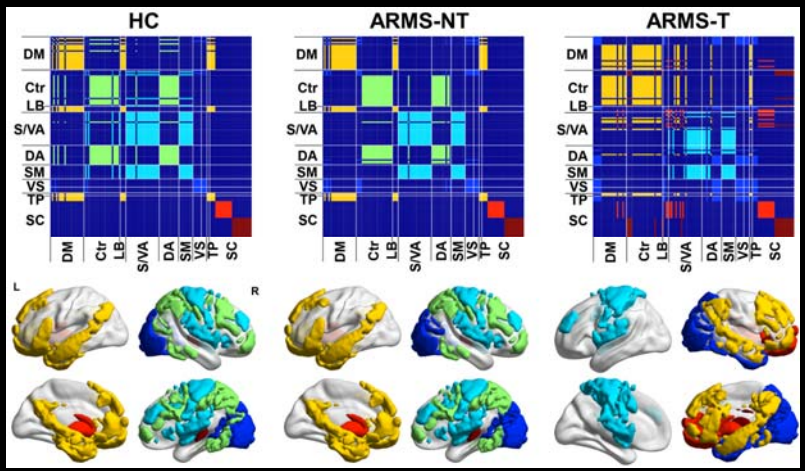
(Bullmore et al. Nat Rev Neurosci 2009)





Wang et al, Cerebral Cortex 2017

Altered network community structures in ARMS-T but not in ARMS-NT



- Default mode network merged with executive control network
- Salience network became fragmented. Ventral part merged with subcortical regions. Dorsal part merged with sensory motor network.

Wang et al, Cerebral Cortex 2017

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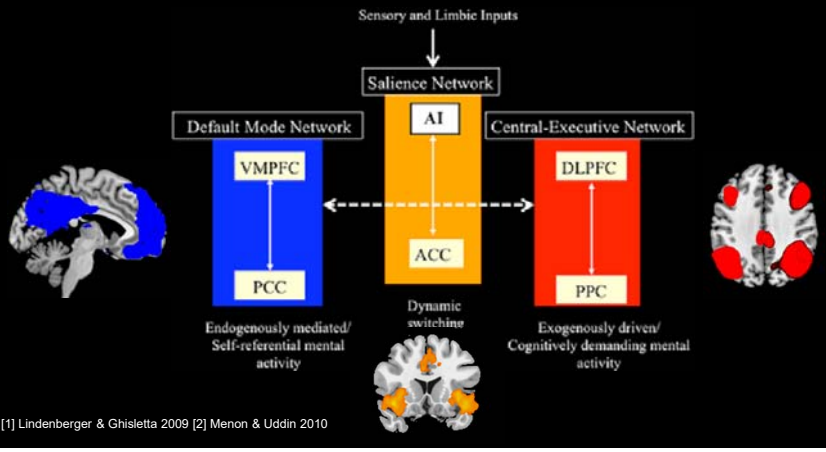
Age-related changes in functional connectivity observed in 'high-level' ICNs

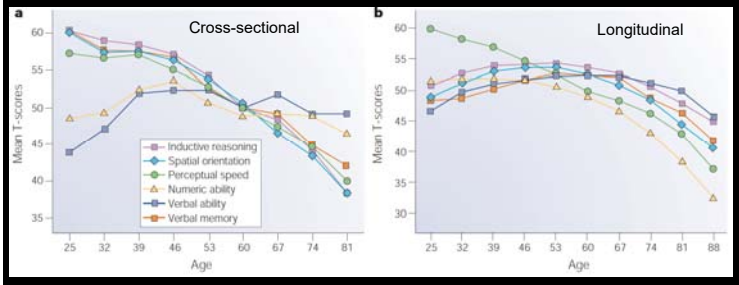
- Age-related cognitive decline ←→'high' level ICNs
  - Default mode network (DMN)
  - Executive control network (ECN)
  - Salience network (SN)

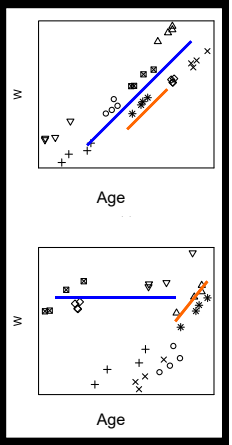


[1] Lindenberger & Ghisletta 2009 [2] Menon & Uddin 2010

The need for longitudinal studies

- Cross-sectional and longitudinal results can disagree
  - Age-related individual differences
  - Within-subject time-dependent change

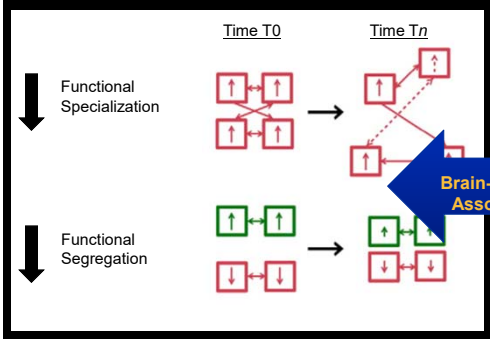


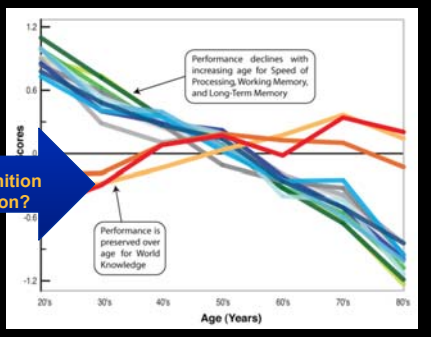


Hedden et al, Nature Neuroscience, 2004

Longitudinal functional connectivity in ageing → cognitive decline

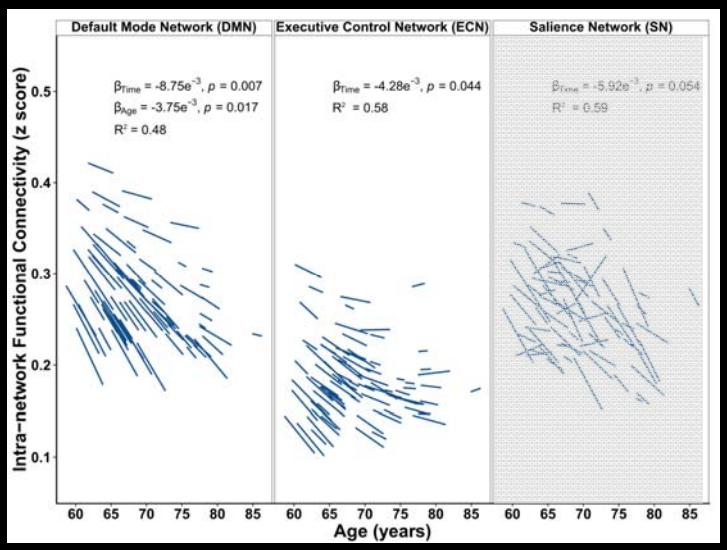
ICN Functional Connectivity **Cognition**

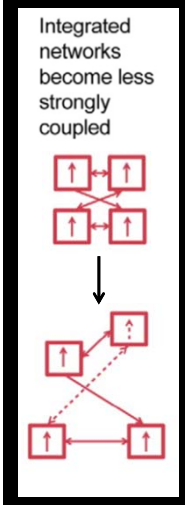




Singapore Longitudinal Ageing Brain Study (S-LABS, 2009-)
78 Healthy older adults (56 – 85 years old)
MMSE >= 26, GDS < 4
no history of neurological /cerebrovascular/cardiovascular disorder

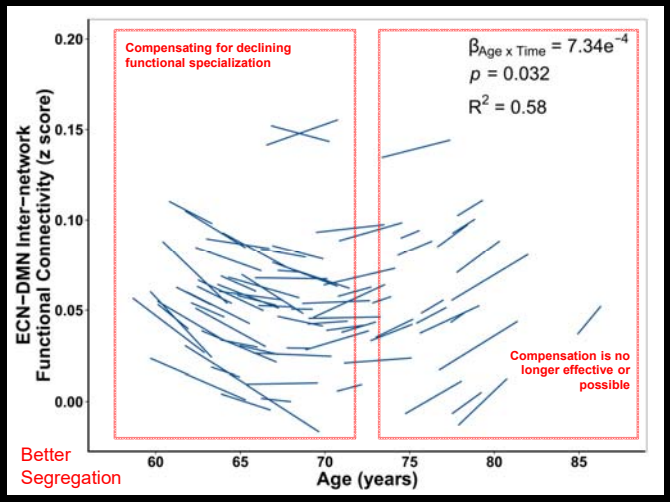
Ageing is associated with decline in functional specialization

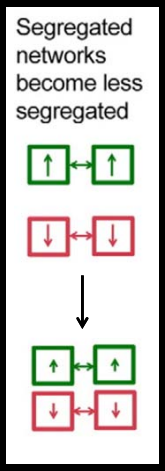




Adjusted for gender, education, grey matter reduction, motion

Ageing is associated with decline in functional segregation

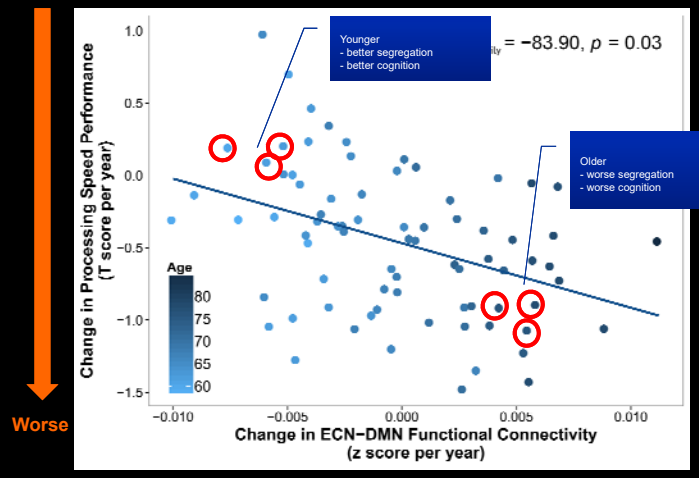




Adjusted for gender, education, grey matter reduction, motion

Ng et al, Neuroimage 2016

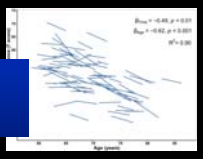
Decline in functional segregation is associated with decline in processing speed

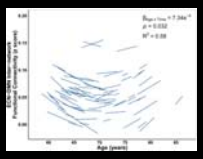


Worse

Worse

Processing speed longitudinal change

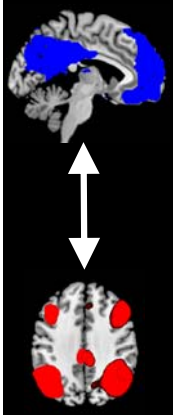


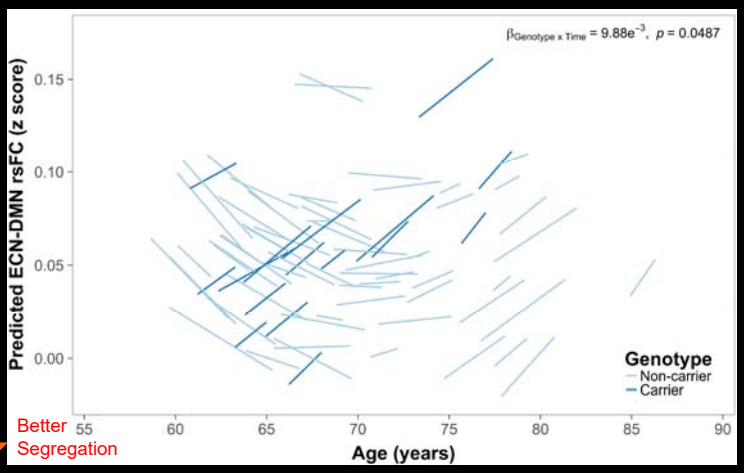


ECN-DMN connectivity longitudinal change

Ng et al. (2016) NeuroImage

The effect of APOE4 on longitudinal trajectory of functional connectivity in healthy old adults



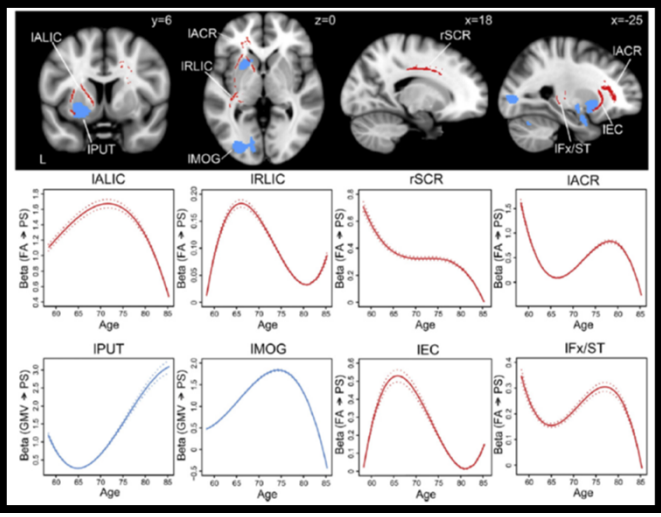


Better Segregation

Ng and Qiu et al, 2017 (HBM, revision submitted)

Differential age-dependent associations of grey matter volume and white matter integrity with processing speed in ageing

Sparse varying coefficient model (Daye et al, 2012)



Hong et al, Neuroimage 2015

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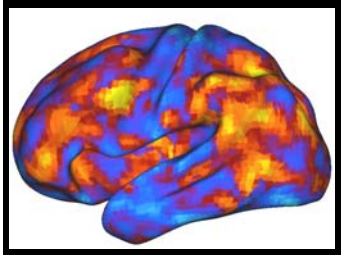
Fluctuations in brain connectivity

Link to changes in behavioral states?



?

Dynamic Connectivity States (DCS)

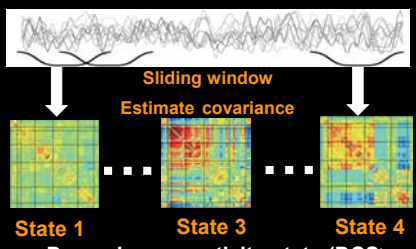
Task free fMRI

4-D dataset

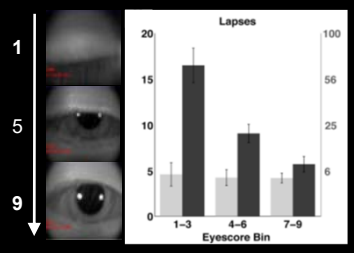
Dynamic connectivity states (DCS)

- Questions?
  - Mechanism and functional significance of DCS
  - How do DCS relate to behavioral performance
- How to evaluate mental microstates without intrusion?
  - Spontaneous eyelid closure (SEC) in sleep deprivation → a proxy for vigilance state

Dynamic functional connectivity

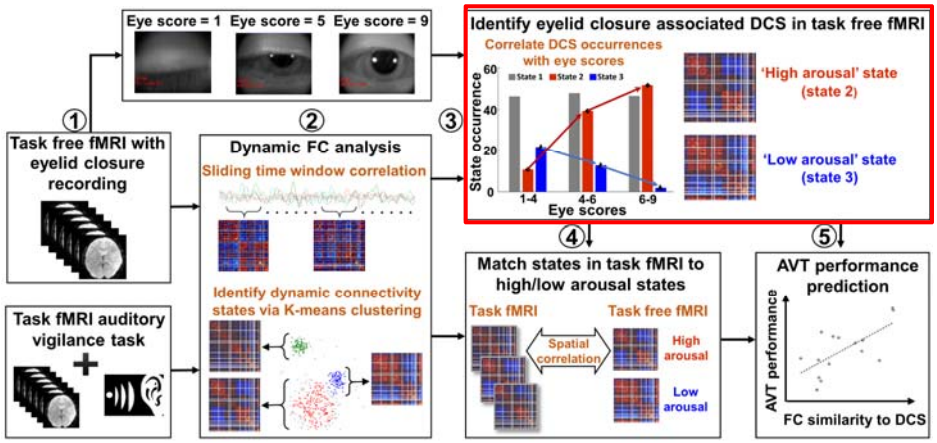


SEC vs task performance

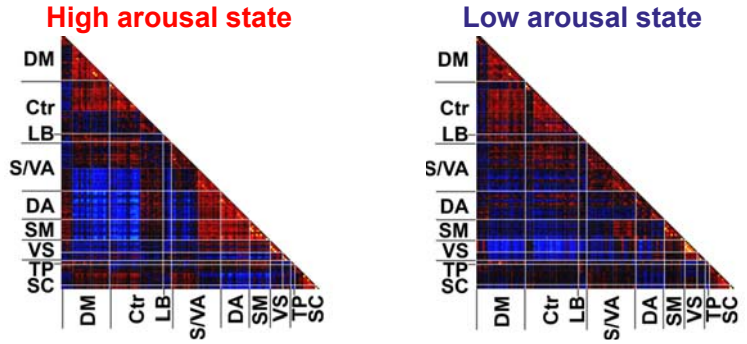


Allen et al., 2012; Hutchison et al., 2013; Calhoun et al., 2014

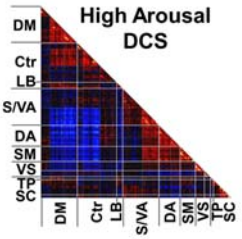
Study design

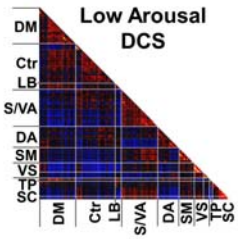


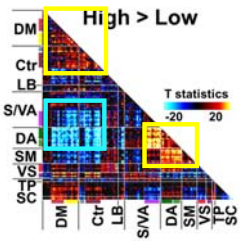
Dynamic connectivity states associated with spontaneous eyelid closure at rest



High and low arousal DCS show within-network and between-network differences

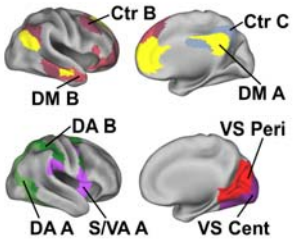


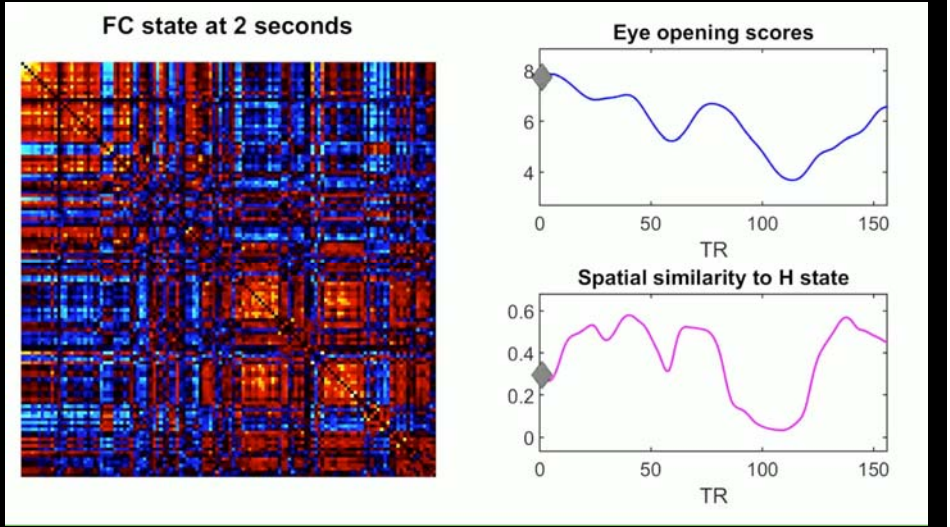




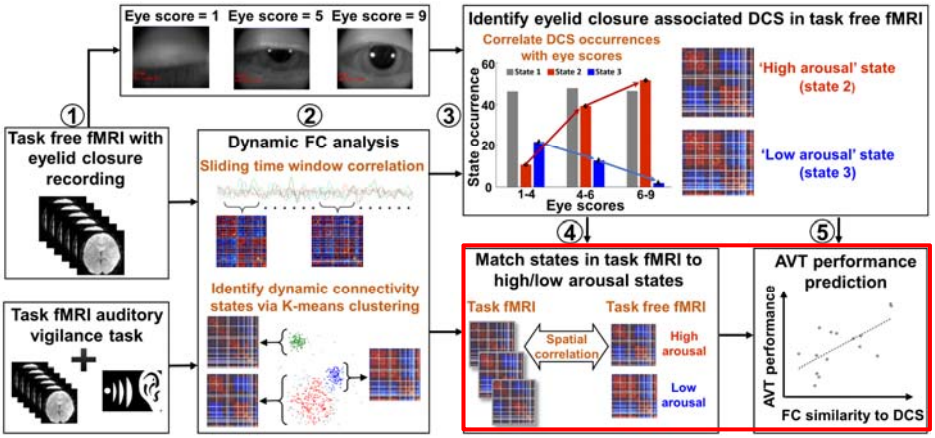
- High > Low:
  - Intra: Default, control, and attention ⬆
  - Inter: Attention and somatomotor ⬆
  - Anti-correlation (Default and attention) ⬆

Wang et al, PNAS 2016



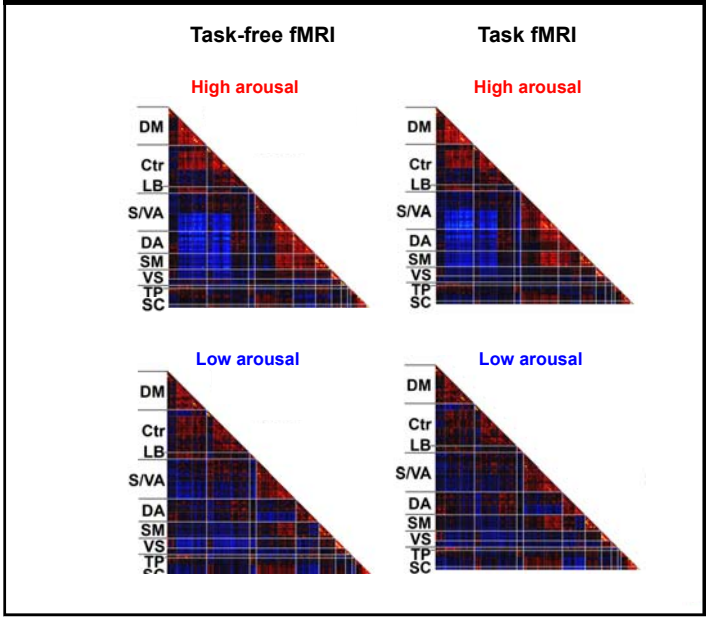


Study schematic

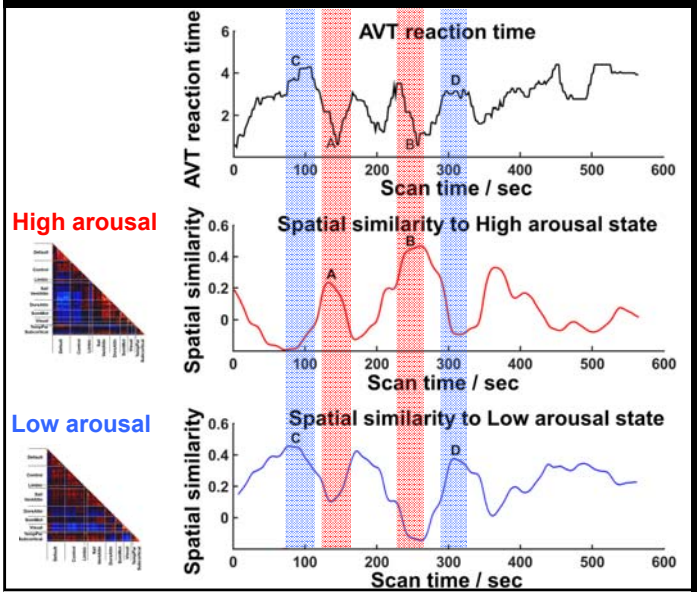


Task fMRI Dynamic connectivity state (DCS)

State occurrence is associated with individual difference in vigilance



DCS is associated with temporal fluctuations in vigilance performance

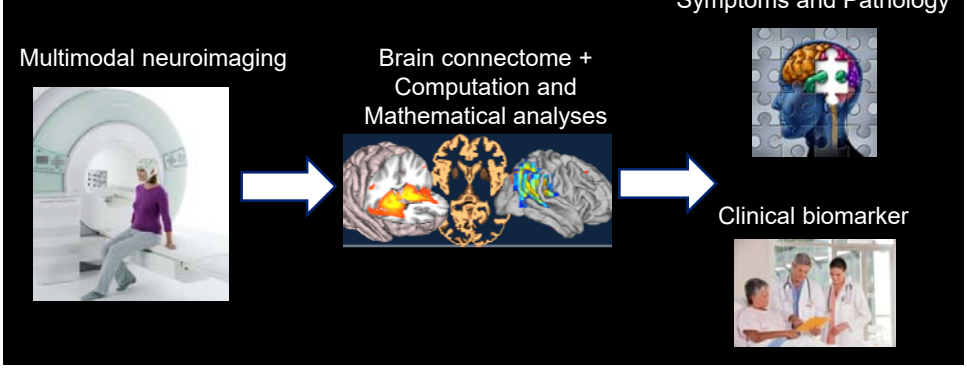


Wang et al, PNAS 2016

Future directions

Need computational and mathematical approach for high-dimensional data

1. Perform early detection
2. Predict neuropathology and behavioral changes
3. Track disease severity and treatment response longitudinally
4. Reveal disease mechanism



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