CARE Experts Webinar

Brain network breakdown related to cognitive decline in ageing and neurodegenerative disorders

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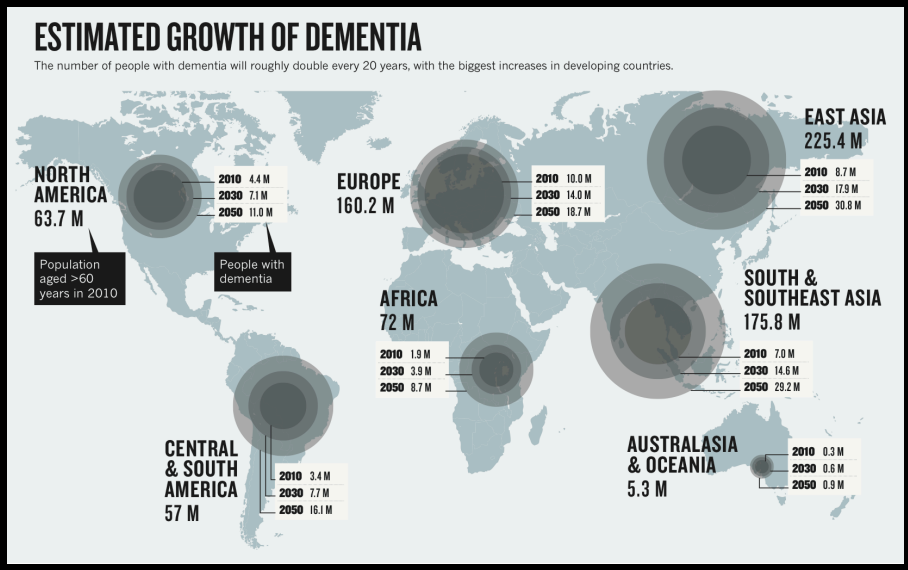
July 8th, 2020

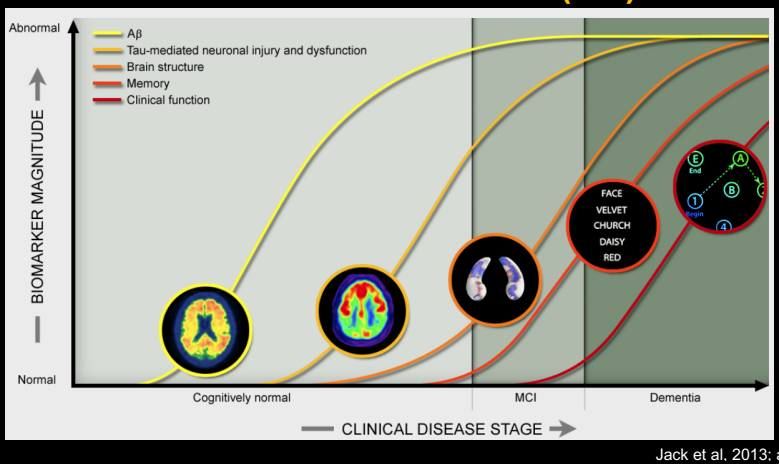
Prevalence of dementia



Abbott, Nature 2011

1. Network-based neurodegeneration using network-sensitive imaging
2. Network dysfunctions in neurodegenerative and cerebrovascular diseases
   - Detect symptom-specific changes in dementia subtypes
   - Track longitudinal changes in pre-dementia stage: risk factors
   - Reveal disease mechanism and monitor disease progression/treatment response

Alzheimer's disease (AD)

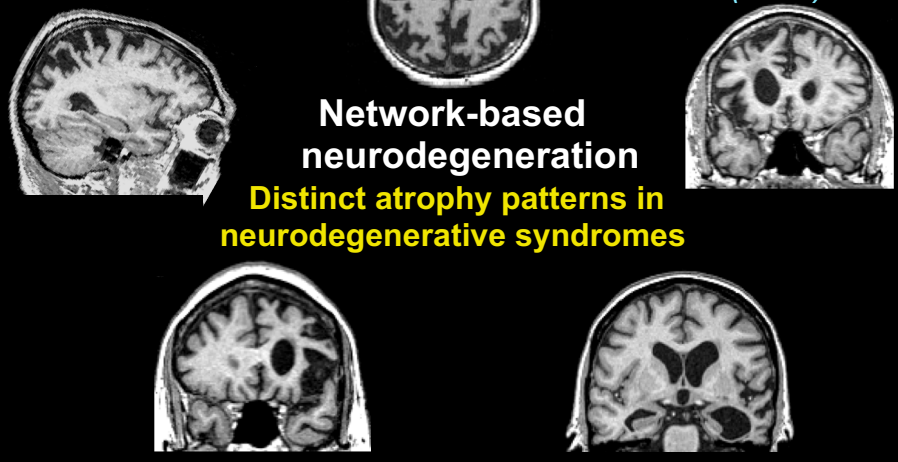


Jack et al, 2013; adni.loni.usc.edu

Alzheimer's disease (AD)

Corticobasal Syndrome (CBS)

Behavioral Variant Frontotemporal Dementia (bvFTD)



Network-based neurodegeneration

Distinct atrophy patterns in neurodegenerative syndromes

Progressive Nonfluent Aphasia (PNFA)

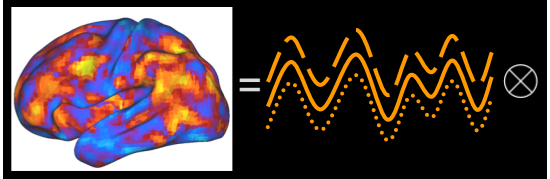
Semantic Dementia (SD)

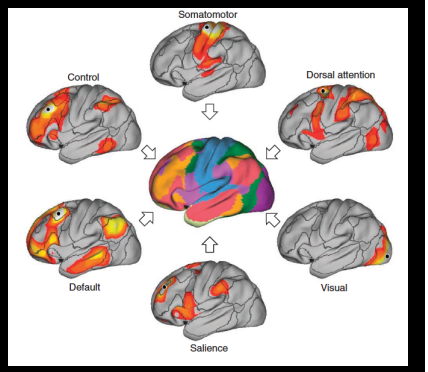
Image courtesy of William Seeley, UCSF

L

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)



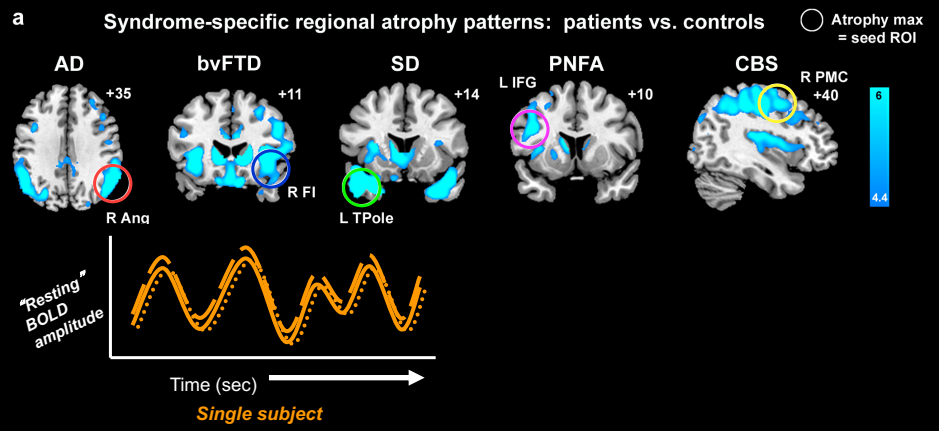


4D fMRI **Time-series** **ICN spatial maps**

Video courtesy of Vincent

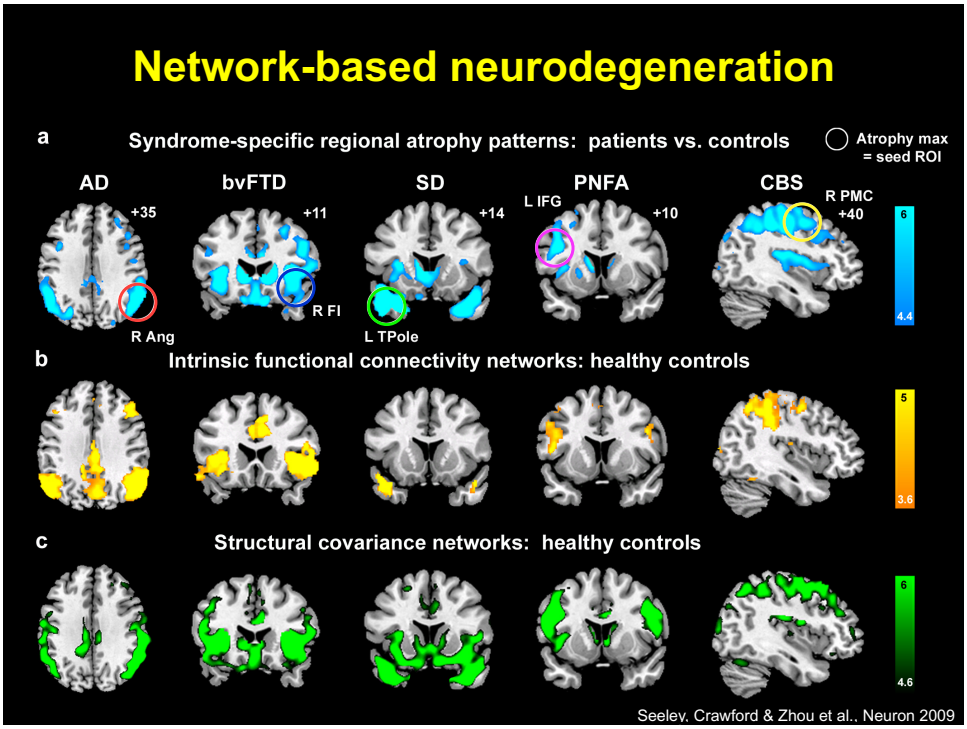
Biswal et al., 1995; Smith et al., 2009; Yeo et al., 2011; Buckner et al., 2013

Syndrome-specific atrophy patterns mirror functional ICNs in healthy controls



Seeley, Crawford & Zhou et al., Neuron 2009

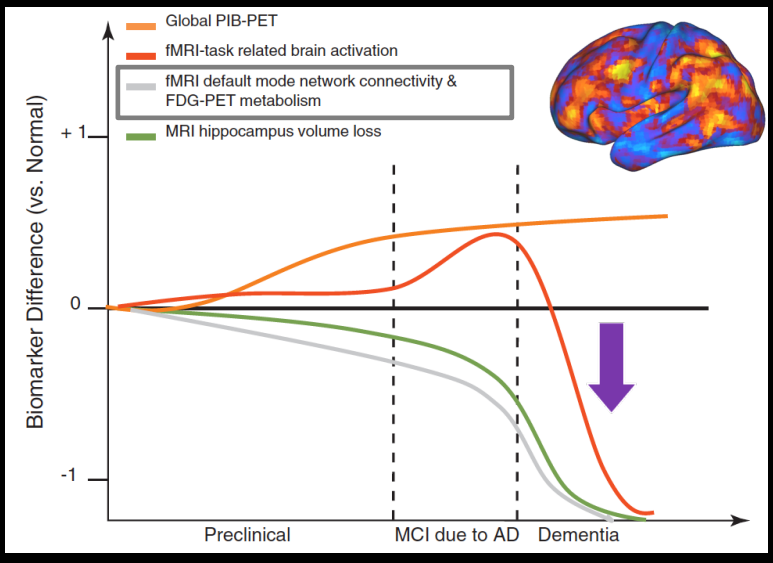
Network-based neurodegeneration



Seeley, Crawford & Zhou et al., Neuron 2009

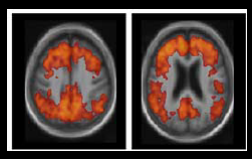
Network breakdown in neurodegenerative and cerebrovascular diseases

Detect symptom-specific changes in dementia subtypes

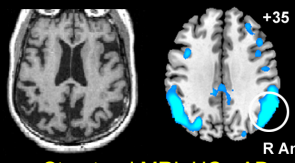


Jack et al, 2013; Ewers et al., 2011

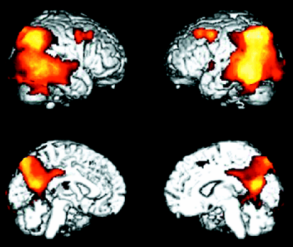
Molecular, structural and functional characterization of Alzheimer's disease (AD)



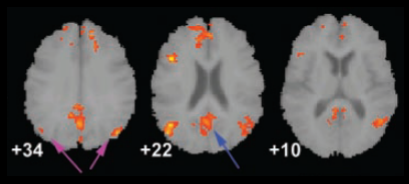
PIB-PET Amyloid: AD
Increased amyloid deposition in AD



Structural MRI: HC >AD
Default mode network atrophy in AD



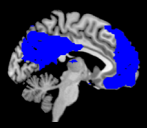
FDG-PET: HC > AD
Hypometabolism in AD

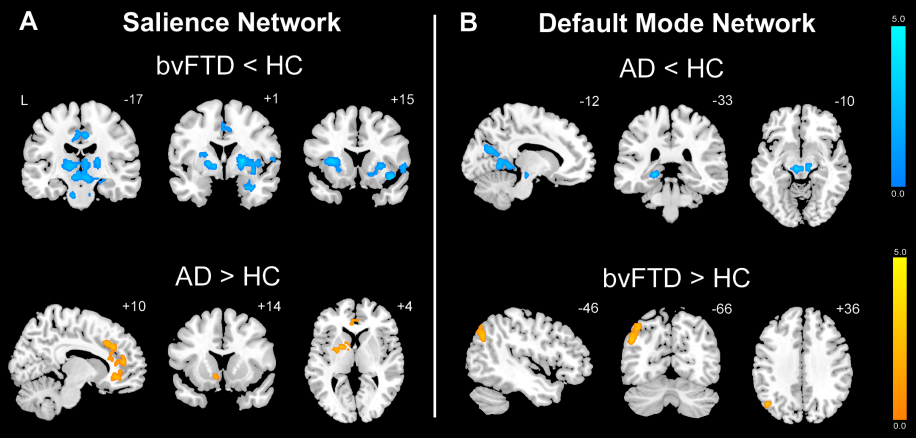


Task-free fMRI: HC > mild AD
Reduced default mode network connectivity in AD

Alexander, J Psy. 2002; Greicius, PNAS, 2004; Buckner, J Neuro. 2005; Seeley, Neuron 2009; Zhou, Brain 2010; Zhou, Neuron 2012

BvFTD and AD: Divergent functional connectivity changes in the salience and default networks

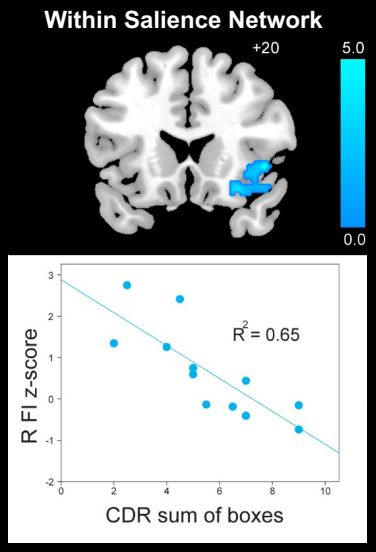




p < 0.05, height & extent corrected

Zhou et al, Brain 2010

Salience network functional connectivity tracks disease severity

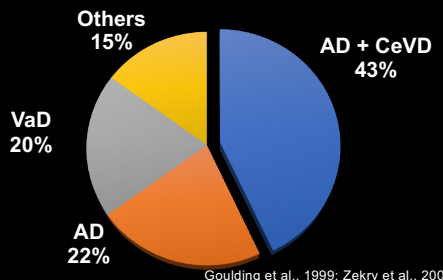


Zhou et al, Brain 2010

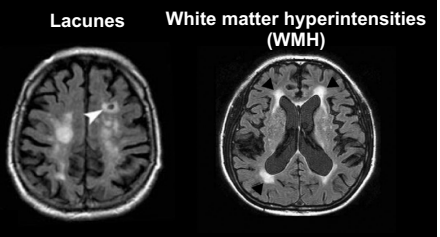
Joanna Chong

AD and Cerebrovascular disease (CeVD): Additive effects on brain networks?

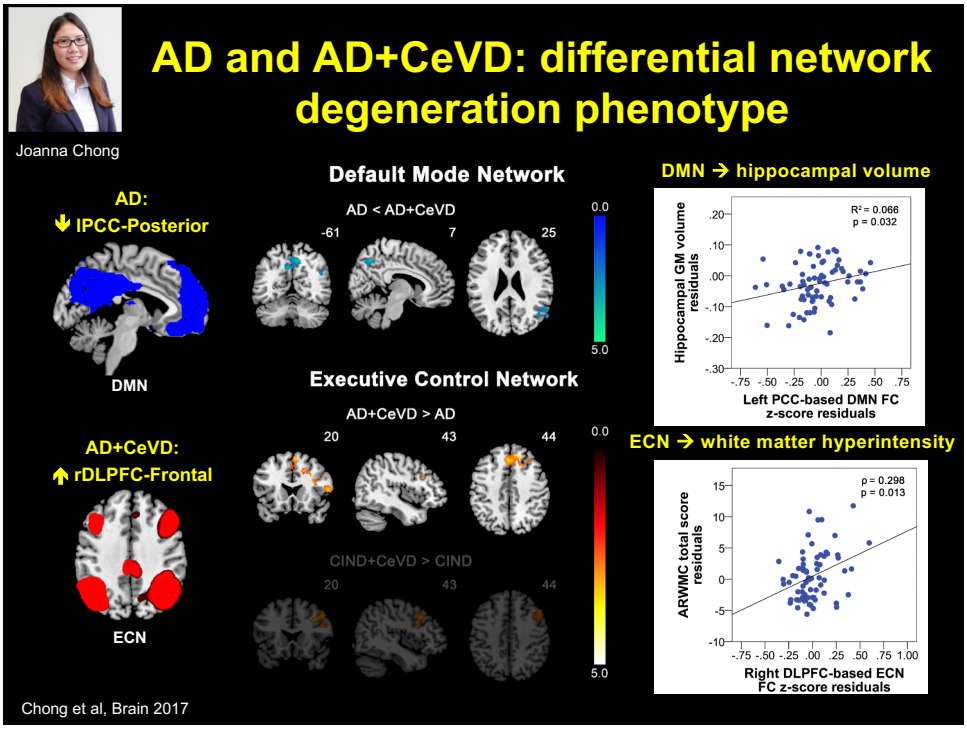
- CeVD and AD are suggested to have additive effects on cognitive decline
- For same clinical severity:
  - AD-only: more severe AD pathology
  - AD+CeVD: CeVD pathology + less severe AD pathology
- What are network changes in AD with and without CeVD?

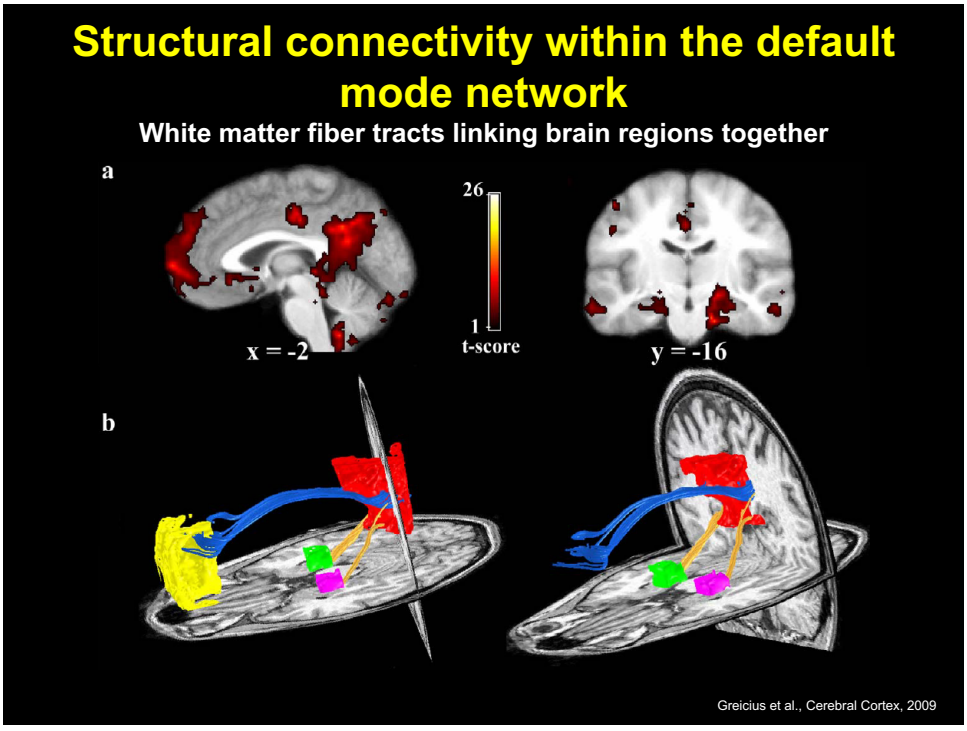


Goulding et al., 1999; Zekry et al., 2002; Toledo et al., 2013

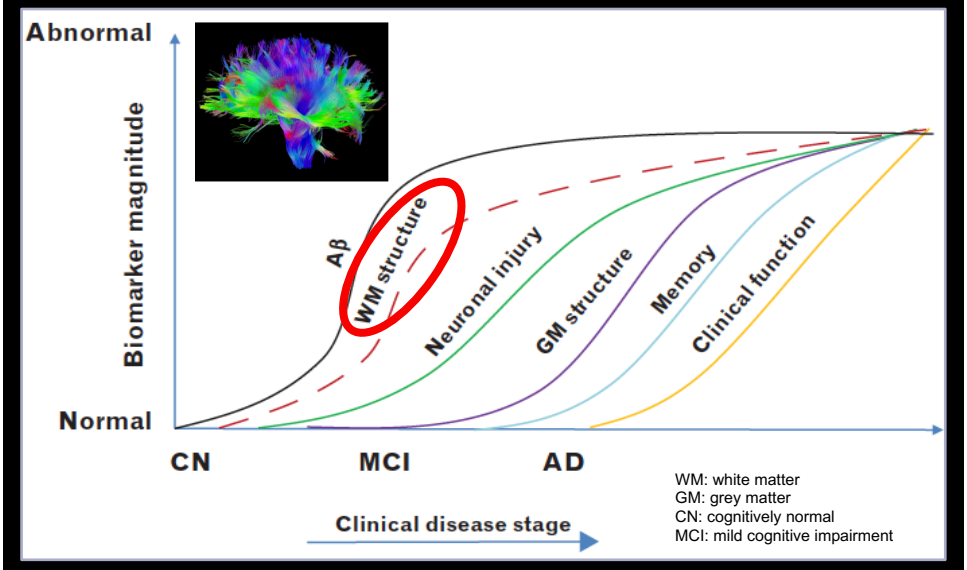


Kim et al., Biol Psychiatry (2008)


AD and AD+CeVD: differential network degeneration phenotype
Joanna Chong
Default Mode Network
AD: ↓ IPCC-Posterior
AD < AD+CeVD
-61
7
25
0.0
5.0
DMN
Executive Control Network
AD+CeVD: ↑ rDLPFC-Frontal
AD+CeVD > AD
20
43
44
0.0
5.0
ECN
CIND+CeVD > CIND
20
43
44
DMN → hippocampal volume
Hippocampal GM volume residuals
R² = 0.066
p = 0.032
Left PCC-based DMN FC z-score residuals
ECN → white matter hyperintensity
ARWMC total score residuals
ρ = 0.298
p = 0.013
Right DLPFC-based ECN FC z-score residuals
Chong et al, Brain 2017

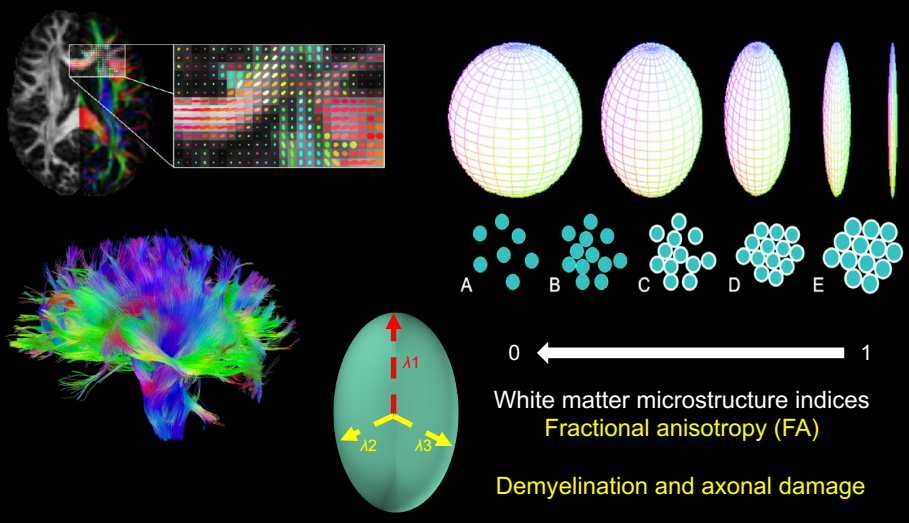

Structural connectivity within the default mode network
White matter fiber tracts linking brain regions together
a
26
1
t-score
x = -2
y = -16
b
Greicius et al., Cerebral Cortex, 2009

White matter degradation in Alzheimer's disease



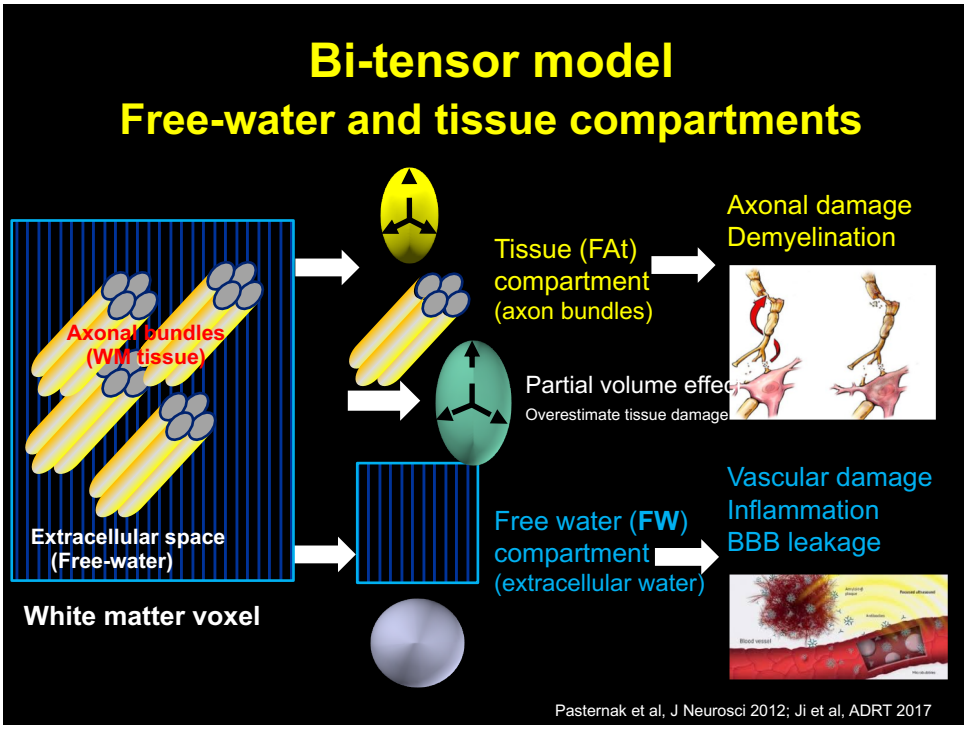
Jack et al., Neuron, 2013; Sachdev et al., Curr. Opin. Psychiatry, 2013

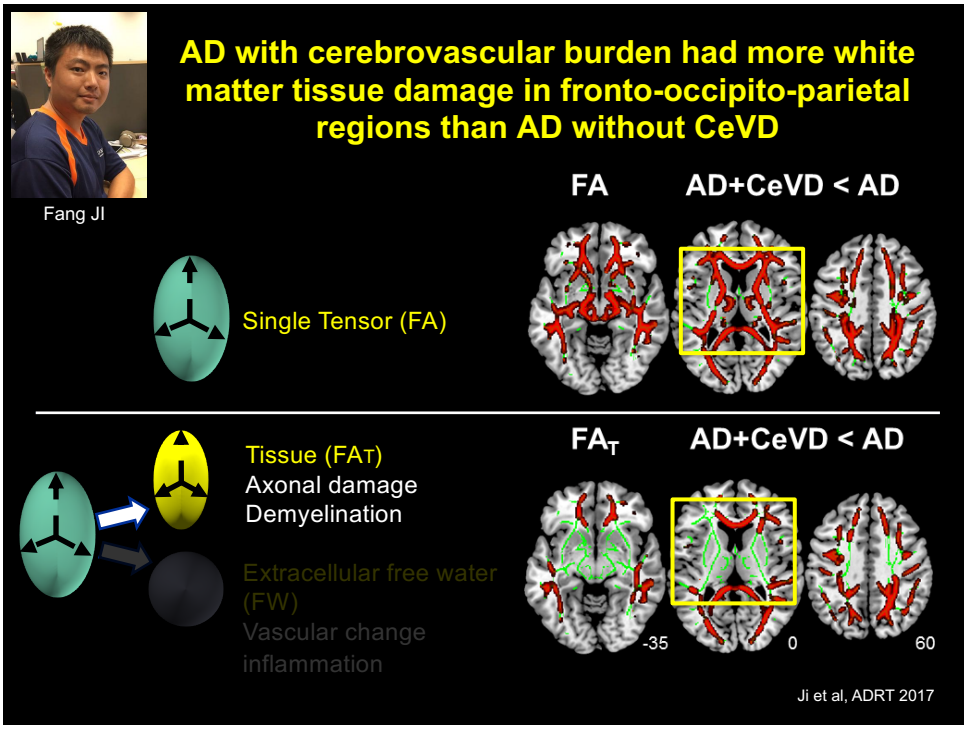
Diffusion tensor imaging (DTI): White matter microstructure



White matter microstructure indices
Fractional anisotropy (FA)

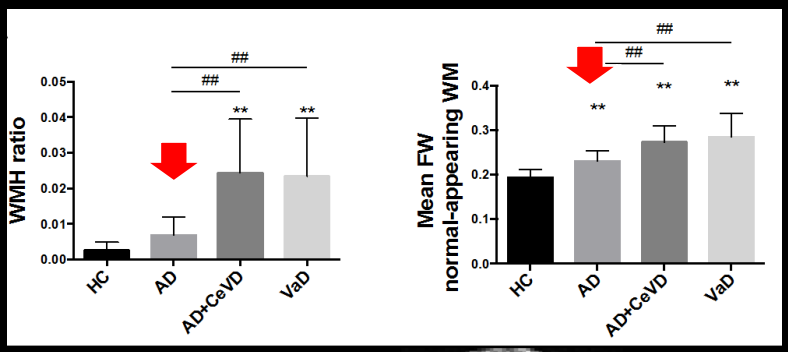
Demyelination and axonal damage

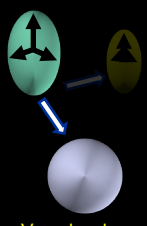

Bi-tensor model
Free-water and tissue compartments
Axonal bundles
(WM tissue)
Extracellular space
(Free-water)
White matter voxel
Tissue (FAt)
compartment
(axon bundles)
Axonal damage
Demyelination
Partial volume effec
Overestimate tissue damage
Free water (FW)
compartment
(extracellular water)
Vascular damage
Inflammation
BBB leakage
Pasternak et al, J Neurosci 2012; Ji et al, ADRT 2017


Fang JI
AD with cerebrovascular burden had more white matter tissue damage in fronto-occipito-parietal regions than AD without CeVD
FA
AD+CeVD < AD
Single Tensor (FA)
FAT
AD+CeVD < AD
Tissue (FAT)
Axonal damage
Demyelination
Extracellular free water (FW)
Vascular change
inflammation
-35
0
60
Ji et al, ADRT 2017

Fang JI

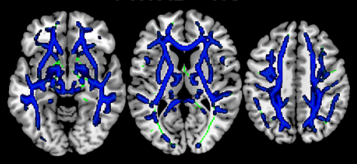
High extracellular FW in normal-appearing WM reflects mild vascular changes in AD

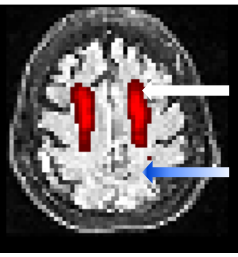




Vascular change inflammation

FW: AD > HC





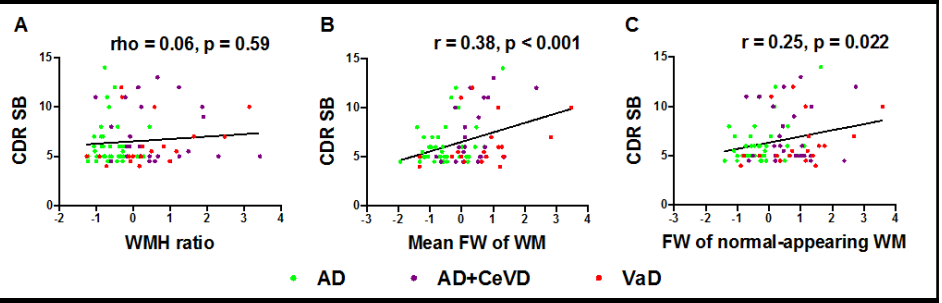
WMH

Normal-appearing WM

Ji et al, ADRT 2017; Scientific Reports 2019

Higher free-water in normal-appearing white matter relates to dementia severity

WMH ratio does not



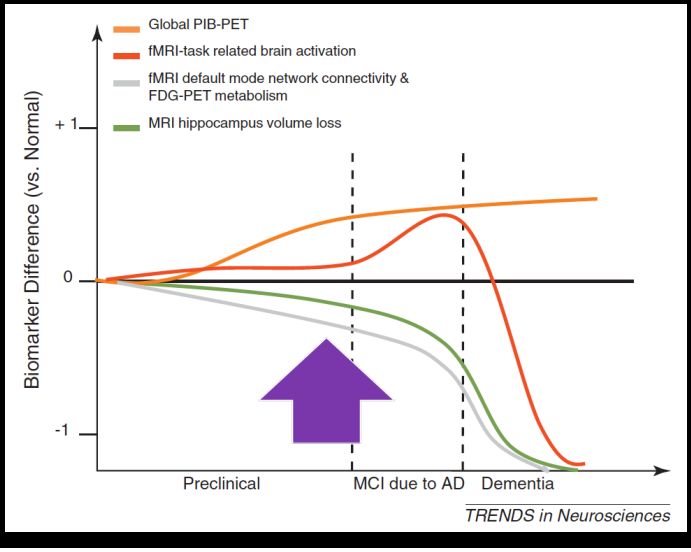
Ji et al, ADRT 2017; Scientific Reports 2019

Summary I

- Network-based neurodegeneration using network-sensitive imaging
  - Each syndrome targets specific large-scale network
  - Syndrome-specific atrophy patterns mirror healthy ICN
  - A direct link between functional ICN and grey matter structure covariance
- Network breakdown in neurodegenerative and cerebrovascular diseases
  - Detect symptom-specific changes in dementia subtypes
    - Structural and functional network phenotype explains clinical variability
  - Track longitudinal changes in pre-dementia stages

Longitudinal brain changes in preclinical and prodromal stage

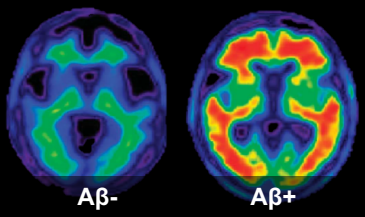
Influence of risk factors and pathology?



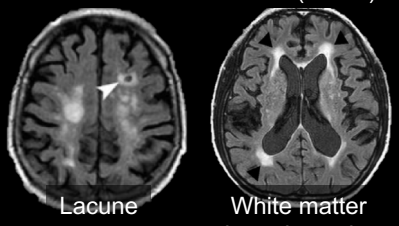
Ewers et al., 2011

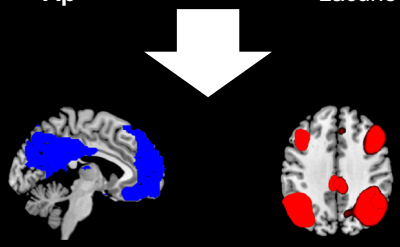
How amyloid and cerebrovascular burden influence network dysfunctions over time?

AD pathology:
Amyloid β



Vascular pathology:
Cerebrovascular disease (CeVD)





Doraiswamy et al, 2014; Goulding et al, 1999; Kim et al, 2008; Toledo et al, 2013; Zekry et al, 2002

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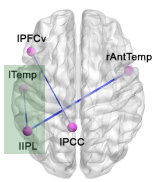
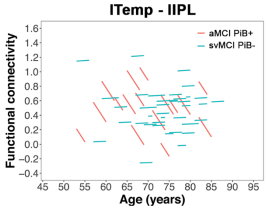
Amyloid and CeVD burden had differential effects on longitudinal FC changes in prodromal dementia

Default Mode Network

aMCI Aβ+ < svMCI Aβ-

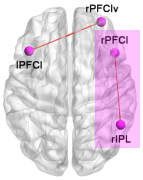


lTemp - lIPL

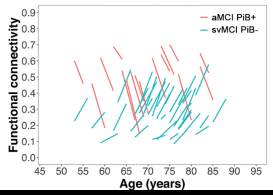


Executive Control Network

svMCI Aβ- > aMCI Aβ+



rPFCl - rIPL



CeVD burden (aMCI vs. svMCI)
×
amyloid burden (PiB)

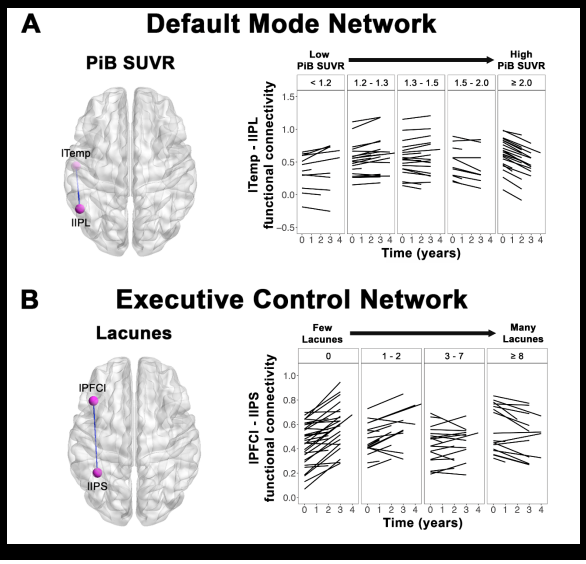
Prodromal patients with 'pure' amyloid burden showed steeper declines in DMN FC

Prodromal patients with 'pure' cerebrovascular burden showed steeper increases in ECN FC

Chong*, Jang*, et al, Neurology 2019

Joanna Chong

Amyloid and CeVD burden had differential effects on longitudinal FC changes in prodromal dementia



CeVD burden (aMCI vs. svMCI)
×
amyloid burden (PiB)

Amyloid burden had an effect on longitudinal DMN FC changes

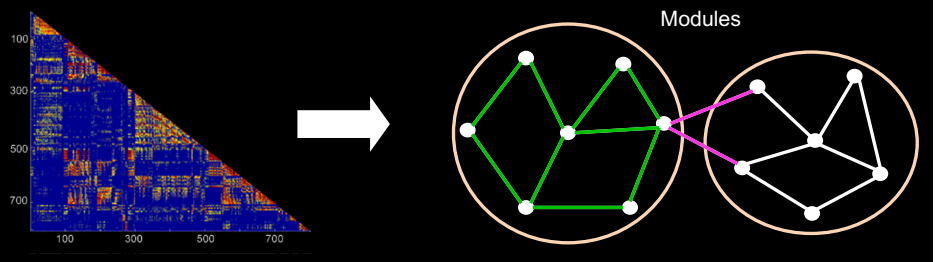
Lacune numbers had an effect on longitudinal ECN FC changes

Chong*, Jang*, et al, Neurology 2019

Modular organization of the brain

Functional specialization
High within-network functional connectivity

Functional segregation
Low between-network functional connectivity

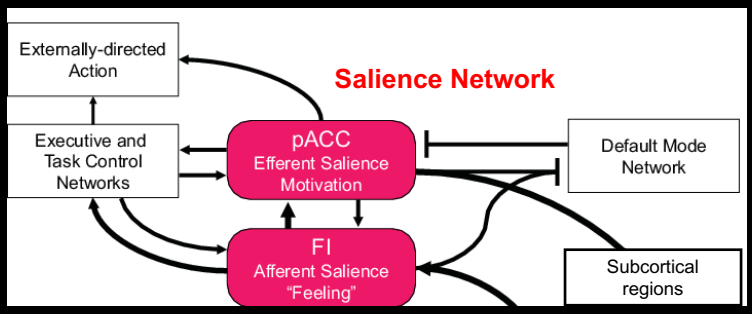


Zhou et al, Neuron 2012

Bullmore & Sporns, Nat Rev Neurosci (2012)
Meunier, Front Neuroinform (2009)

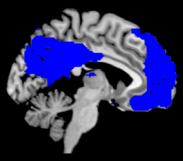
Higher-order cognitive networks

Within and between network connectivity



Executive control network

Salience network



Default mode network

Zhou & Seeley, Biological Psychiatry, 2014

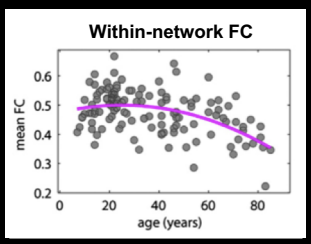
Loss of functional segregation and specialization with age

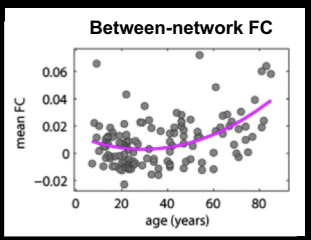
Functional specialization

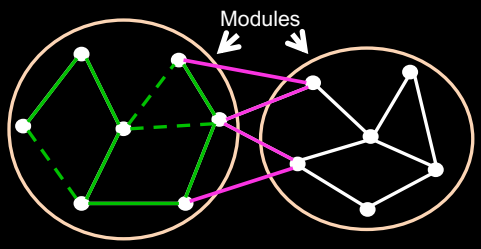
Reduced within-network FC

Functional segregation

Increased between-network FC







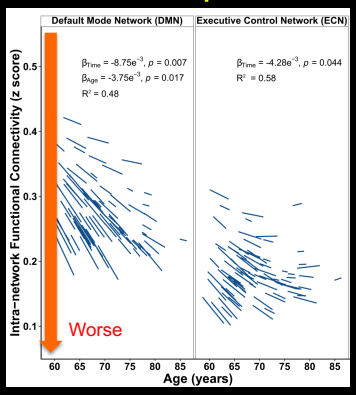
Bullmore & Sporns, Nat Rev Neurosci (2012)
Meunier, Front Neuroinform (2009)

Betzel et al., Neuroimage (2014)

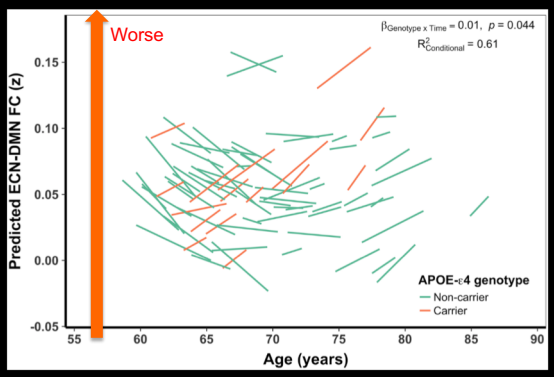
Longitudinal loss of functional specialization and segregation in cognitively normal older adults

The effect of *APOE* ε4

Intra-network specialization



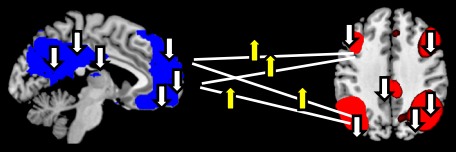
Inter-network segregation



Ng* and Qiu* et al, HBM 2018

Ng et al. NeuroImage 2016

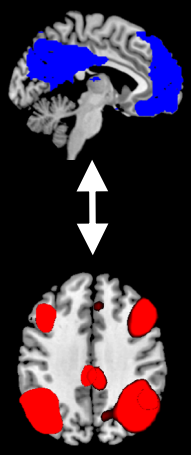
Eric KK Ng Yingwei Qiu



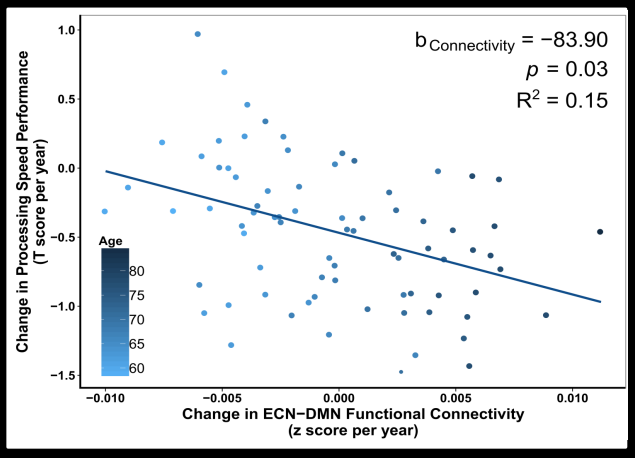
Default mode Executive control

Greater loss of functional segregation relate to faster decline in processing speed

Default mode



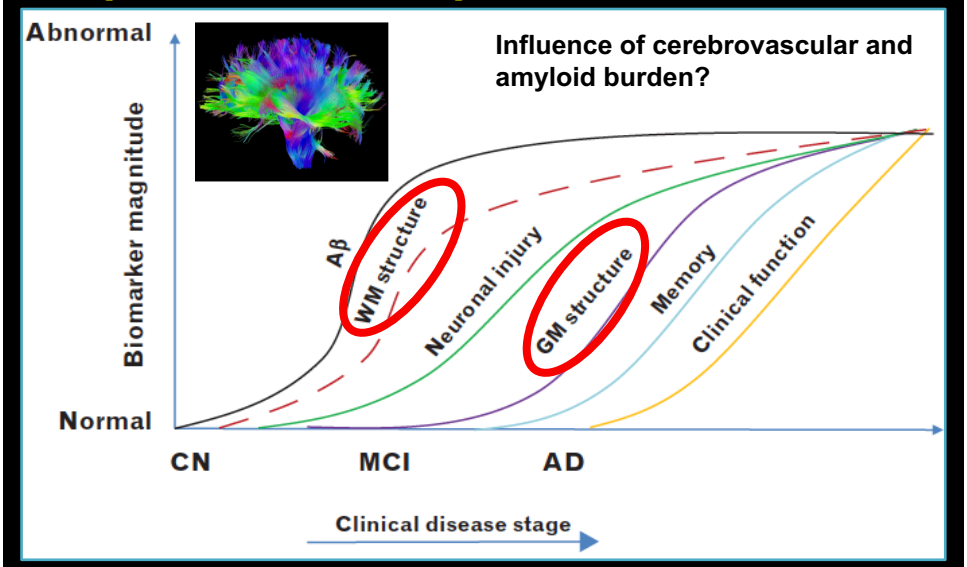
Executive control

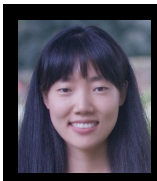


Results adjusted for rate of change in grey matter volume

Ng et al. NeuroImage 2016

Early grey and white matter degradation in preclinical and prodromal dementia

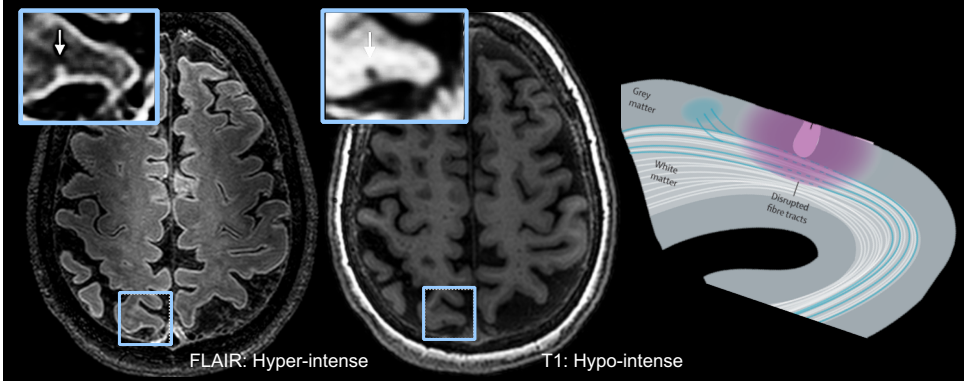




Liwen ZHANG

Cortical cerebral microinfarcts affect structural network topology in high-level cognitive networks in prodromal AD

- A novel marker now possible to spot in human *in vivo* at 3T
- 43% in AD vs 24% in controls
- Associated with cognitive impairment controlled for other markers
- CMI impaired white matter tracts in animal studies

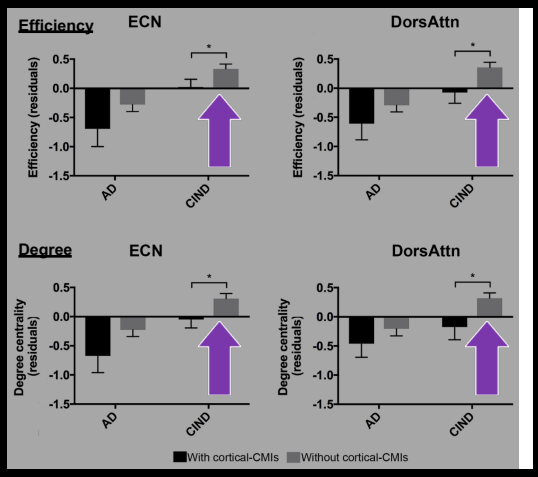


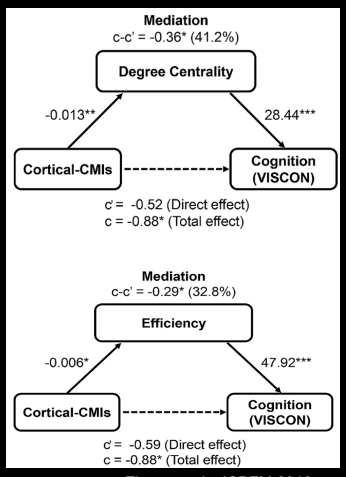
van Veluw et al, 2015, 2017; Brundel et al, 2012; Summers et al, 2017

Liwen ZHANG

Cortical cerebral microinfarcts (CMI) affect structural network topology in high-level cognitive networks in prodromal AD

- Lower network efficiency and degree centrality in prodromal AD with CMI
- Structural network breakdown mediated CMI-cognition association

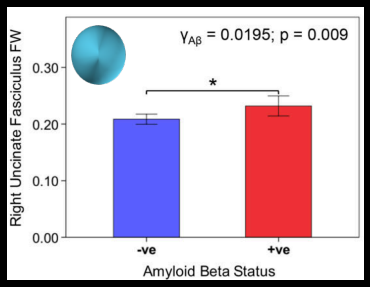


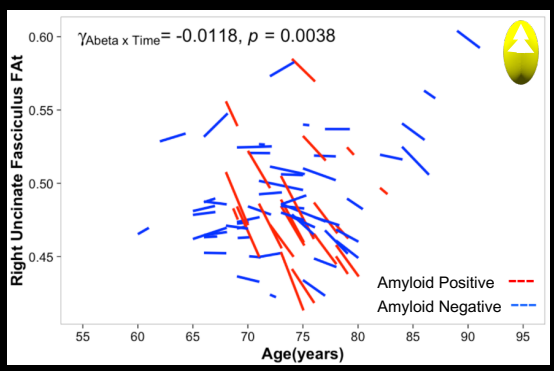


Zhang et al., JCBFM 2019

Ashwati VIPIN

Amyloid burden accelerates white matter tissue degradation in right uncinate fasciculus in cognitively normal elderly

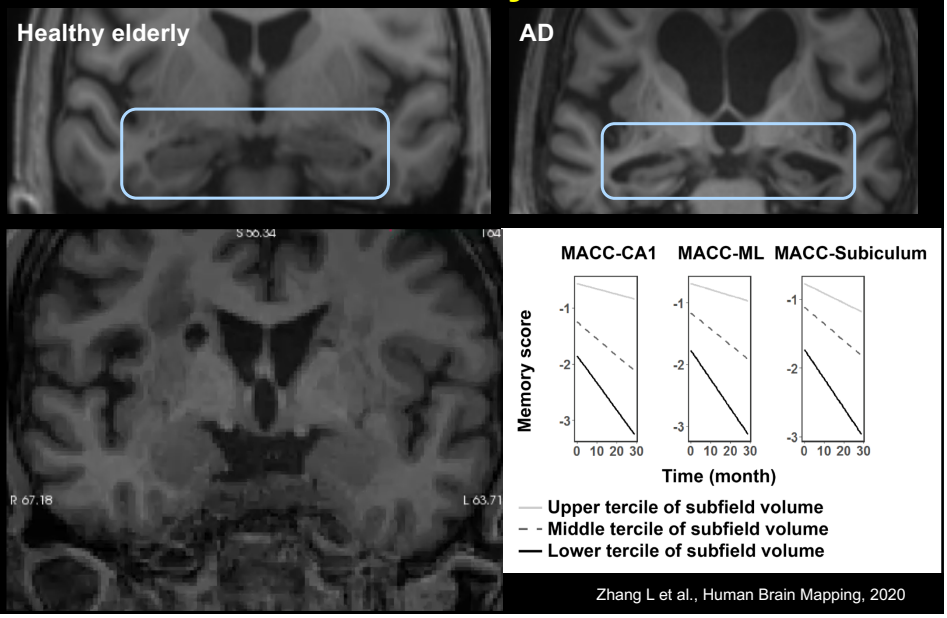




RUNC

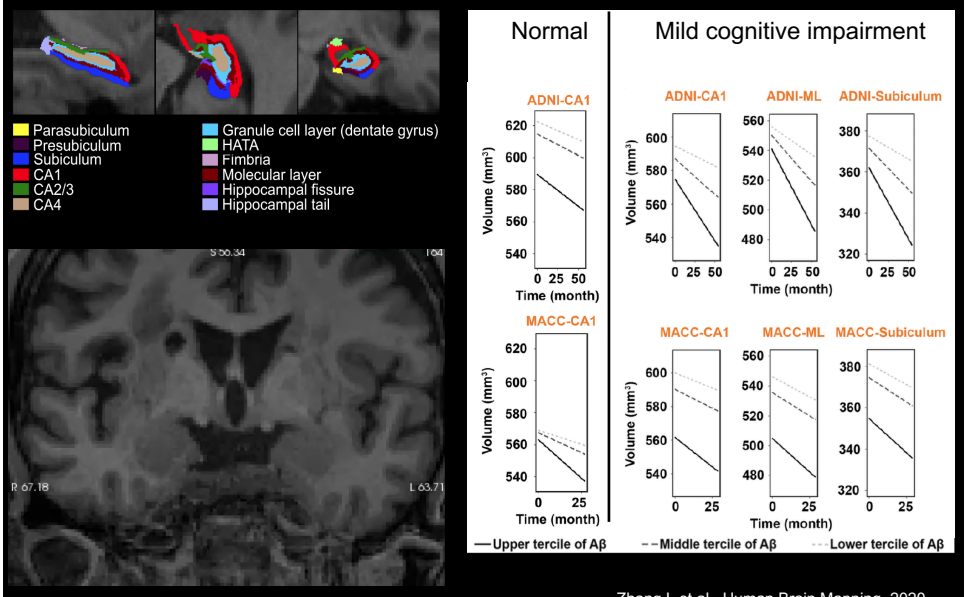
Vipin et al., Human Brain Mapping 2019

Smaller hippocampal volume relates to faster memory decline



Zhang L et al., Human Brain Mapping, 2020

Amyloid burden relates to longitudinal focal-to-widespread hippocampal subfield degeneration in non-demented elderly

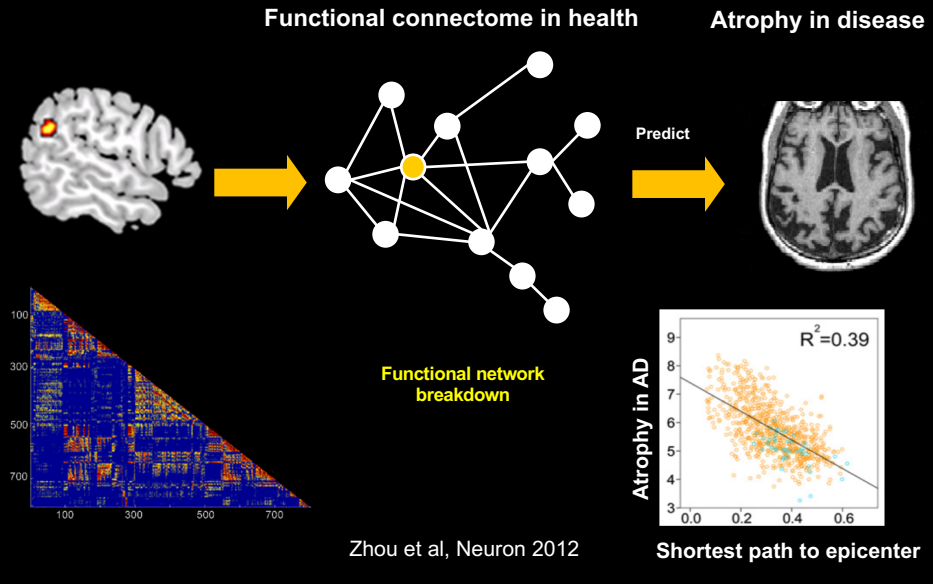


Zhang L et al., Human Brain Mapping, 2020

Summary II

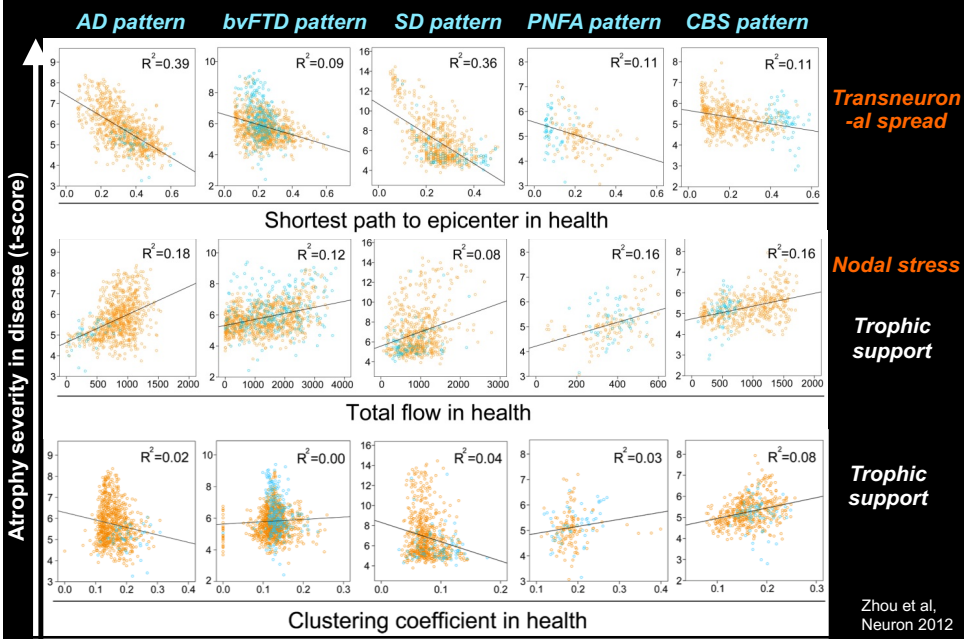
- Network-based neurodegeneration using network-sensitive imaging
- Network dysfunctions in neurodegenerative and cerebrovascular diseases
  - Detect symptom-specific changes in dementia subtypes
    - Structural and functional network phenotype explains clinical variability
  - Track longitudinal changes in pre-dementia stages
    - Specific brain network dysfunctions in preclinical and prodromal AD
    - Risk factors and pathology influence longitudinal trajectories of brain structure and function underlying cognitive decline
  - Reveal disease mechanism; predict behavior, disease progression/treatment response

Predicting disease vulnerability from the healthy brain functional connectome



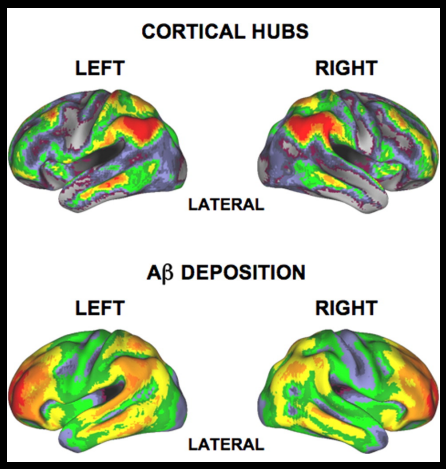
Zhou et al, Neuron 2012

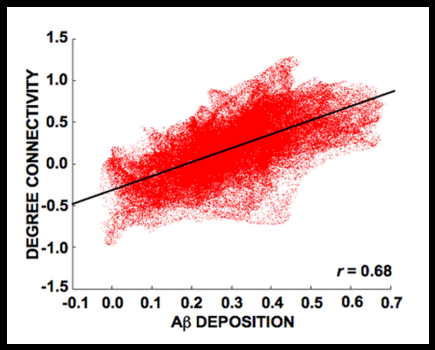
Graph metrics in healthy brain connectivity are related to atrophy severity in disease: Network breakdown



Zhou et al, Neuron 2012

Network cortical hubs have greater amyloid deposition



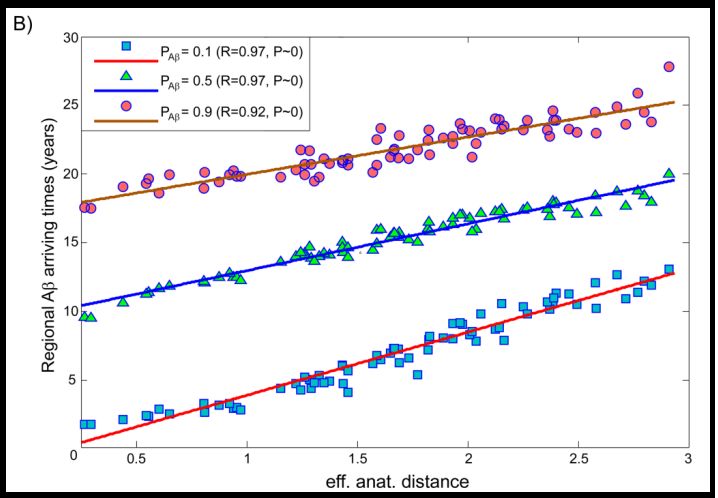


Nodal stress

Buckner et al, J Neurosci, 2009

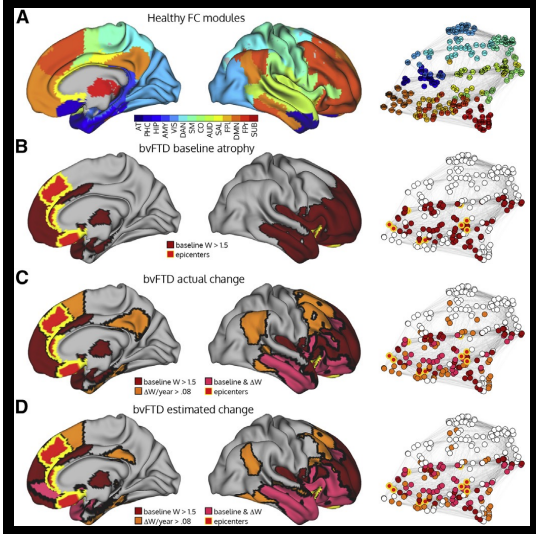
Diffusion-based anatomical distance to outbreak regions modulates the amyloid propagation processes

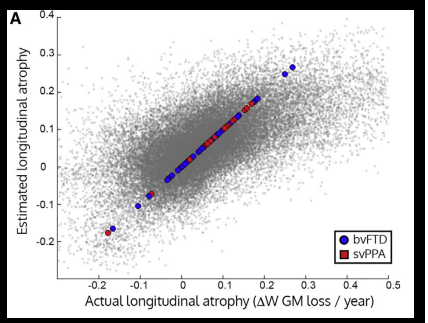
Transneuronal spread



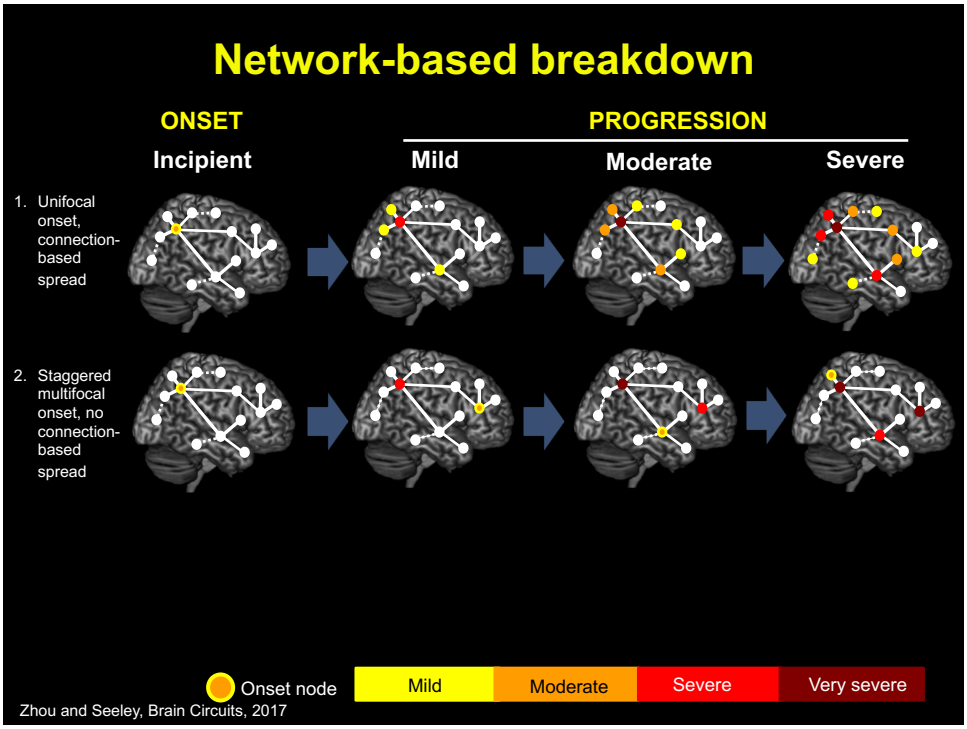
Iturria-Medina et al, PLOS Computational Biology, 2014

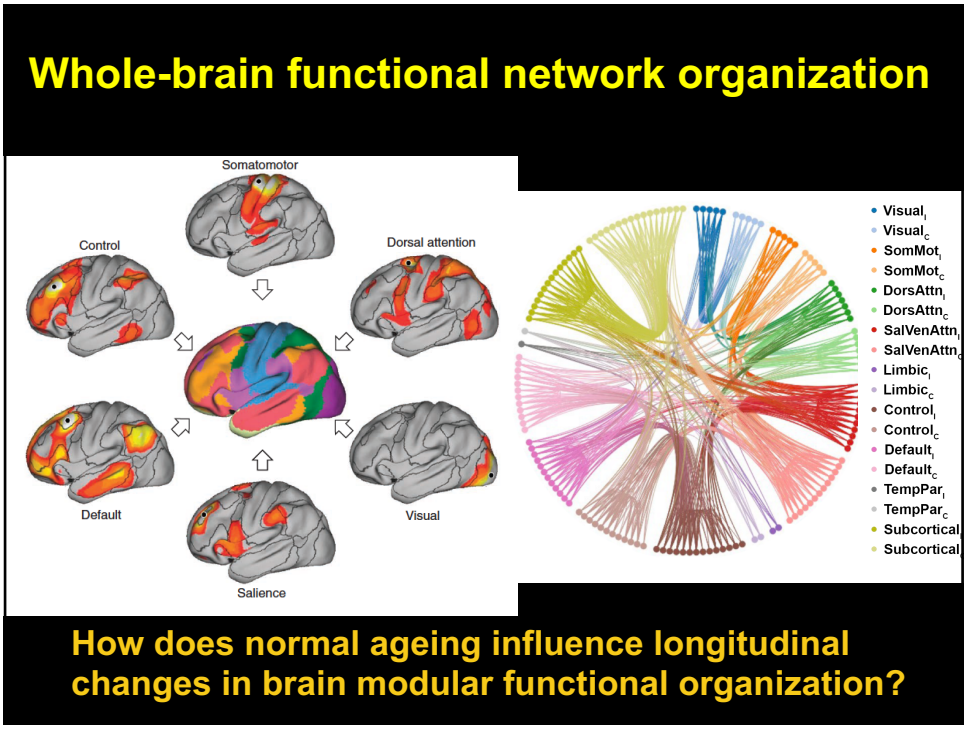
Patient-tailored, connectivity-based forecasts of spreading brain atrophy over time





Brown et al., Neuron 2019

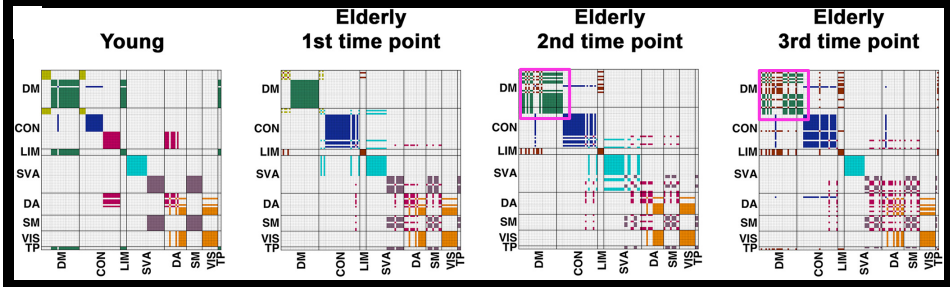

Network-based breakdown
ONSET
PROGRESSION
Incipient
Mild
Moderate
Severe
1. Unifocal onset, connection-based spread
2. Staggered multifocal onset, no connection-based spread
Onset node
Mild
Moderate
Severe
Very severe
Zhou and Seeley, Brain Circuits, 2017


Whole-brain functional network organization
Somatomotor
Control
Dorsal attention
Default
Visual
Salience
Visual$_i$
Visual$_c$
SomMot$_i$
SomMot$_c$
DorsAttn$_i$
DorsAttn$_c$
SalVenAttn$_i$
SalVenAttn$_c$
Limbic$_i$
Limbic$_c$
Control$_i$
Control$_c$
Default$_i$
Default$_c$
TempPar$_i$
TempPar$_c$
Subcortical
Subcortical
How does normal ageing influence longitudinal changes in brain modular functional organization?

Joanna Chong

Elderly showed greater age-related fragmentation of modular structure

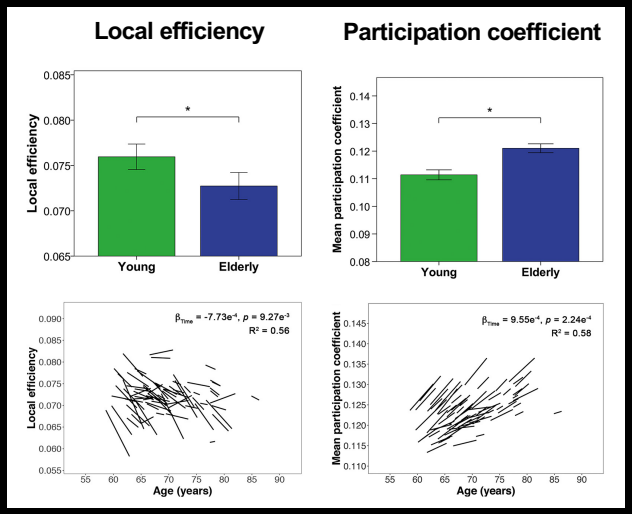
Compared to young adults and with time



Controlled for motion, scan duration, brain template

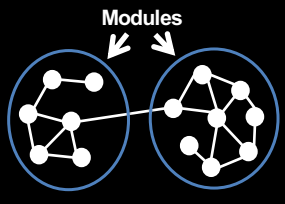
Chong et al., J Neuroscience 2019

Elderly showed cross-sectional and longitudinal declines in network segregation and distinctiveness



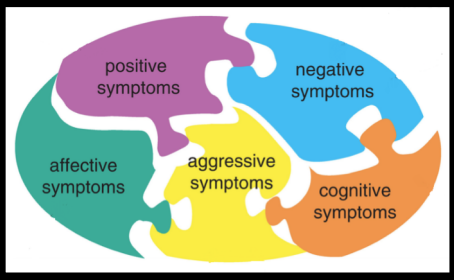
↓ Local efficiency
↓ Network segregation

↑ Participation coefficient
↓ Network distinctiveness



Chong et al., J Neuroscience 2019

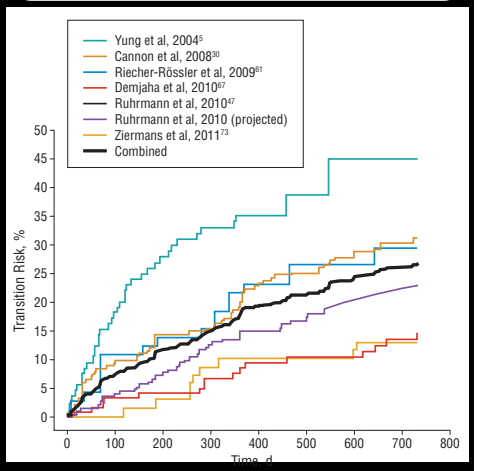
Psychosis prodrome – predicting conversion



(Stahl's essential Psychopharmacology)

At-risk mental state for psychosis (ARMS)

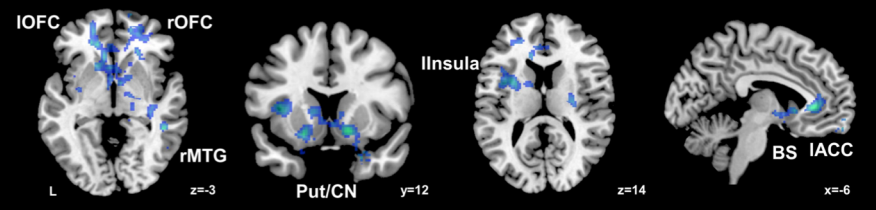
Variable outcomes in ARMS



Fusar-Poli et al. Arch Gen Psychiatry 2012

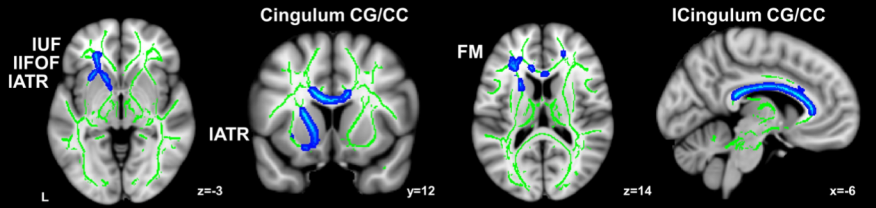
Salience network structural and functional dysconnectivity in ARMS

A Functional Connectivity to left vAI



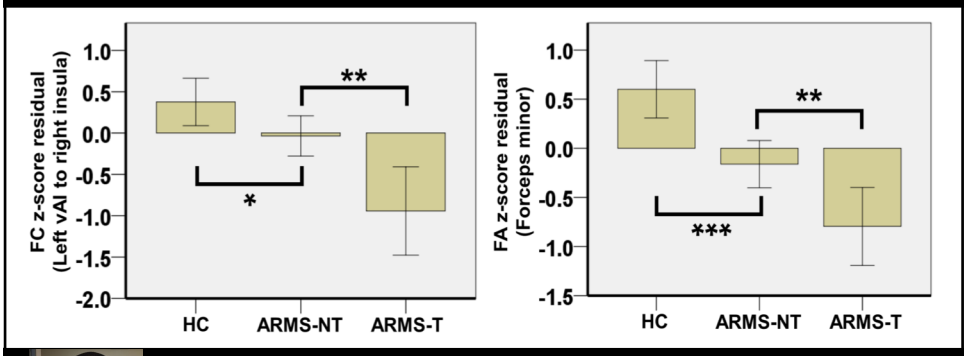
B Fractional Anisotropy

C Axial Diffusivity



Wang et al. Psychol Med 2016

Functional and structural dysconnectivity predicted psychotic conversion in ARMS



Chenhao WANG, MD, PhD

Wang et al. Psychol Med 2016;
Wang et al., Cerebral Cortex 2017

The Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge: Results after 1 Year Follow-up

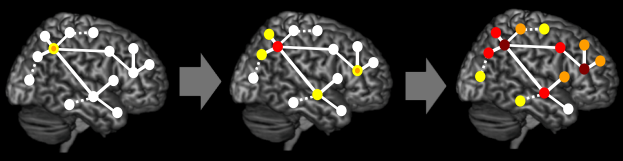
Submission	Overall Rank	Diagnosis Rank	Diagnosis MAUC	Diagnosis BCA	ADAS-Cog13 Rank	ADAS-Cog13 MAE	ADAS-Cog13 WES	ADAS-Cog13 CPA	Ventricles (% ICV) Rank	Ventricles (% ICV) MAE	Ventricles (% ICV) WES	Ventricles (% ICV) CPA
ConsensusMedian	-	-	0.925	**0.857**	-	5.12	5.01	0.28	-	**0.38**	0.33	0.09
Frog	**1**	**1**	**0.931**	0.849	4	4.85	4.74	0.44	10	0.45	0.33	0.47
ConsensusMean	-	-	0.920	0.835	-	**3.75**	**3.54**	**0.00**	-	0.48	0.45	0.13
EMC1-Std	2	8	0.898	0.811	23-24	6.05	5.40	0.45	1-2	0.41	**0.29**	0.43
VikingAI-Sigmoid	3	16	0.875	0.760	7	5.20	5.11	0.02	11-12	0.45	0.35	0.20
EMC1-Custom	4	11	0.892	0.798	23-24	6.05	5.40	0.45	1-2	0.41	**0.29**	0.43
CBIL	5	9	0.897	0.803	15	5.66	5.65	0.37	13	0.46	0.46	0.09
Apocalypse	6	7	0.902	0.827	14	5.57	5.57	0.50	20	0.52	0.52	0.50
GlassFrog-Average	7	4-6	0.902	0.825	8	5.26	5.27	0.26	29	0.68	0.60	0.33
GlassFrog-SM	8	4-6	0.902	0.825	17	5.77	5.92	0.20	21	0.52	0.33	0.20
BORREGOTECMTY	9	19	0.866	0.808	20	5.90	5.82	0.39	5	0.43	0.37	0.40
BenchmarkMixedEffects	-	-	0.846	0.706	-	4.19	4.19	0.31	-	0.56	0.56	0.50
EMC-EB	10	3	0.907	0.805	39	6.75	6.66	0.50	9	0.45	0.40	0.48
lmaUCL-Covariates	11-12	22	0.852	0.760	27	6.28	6.29	0.28	3	0.42	0.41	0.11
CN2L-Average	11-12	27	0.843	0.792	9	5.31	5.31	0.35	16	0.49	0.49	0.33
VikingAI-Logistic	13	20	0.865	0.754	21	6.02	5.91	0.26	11-12	0.45	0.35	0.20

Summary III

- Network-based neurodegeneration using network-sensitive imaging
- Network dysfunctions in neurodegenerative and cerebrovascular diseases
  - Detect symptom-specific changes in dementia subtypes
  - Track longitudinal changes in pre-dementia stages
  - Reveal disease mechanism, monitor treatment response, and predict disease progression

Future directions

Aim for individualized early detection, prognosis, and proactive intervention

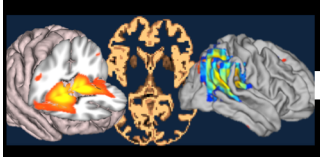


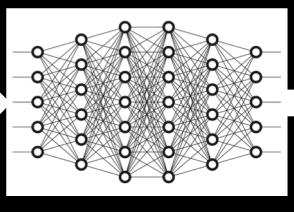
Big data, multimodal, and multivariate approaches
Advancing image acquisition and processing
Interpretability, reliability, and reproducibility

Neuroimaging, Genetic, Blood, CSF, digital…

Computation and statistics Machine learning

Clinical outcomes, Intervention/Pathology





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NMRC National Medical Research Council Singapore

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Thank you!