Exploring Brain Networks in Neurodegenerative Disease

Michael E. Greicius, MD
Functional Imaging in Neuropsychiatric Disorders (FIND) Lab
Department of Neurology and Neurological Sciences
Stanford University School of Medicine
Disclosure

SBGneuro: co-founder/shareholder (resting-state fMRI analysis for clinical trials)
Overview

Network imaging with resting-state fMRI

The default-mode network and Alzheimer’s disease

The salience network and frontotemporal dementia

Future directions
Functional Connectivity with Resting-State fMRI

BOLD Signal

Time

$r = 0.80$

$r = 0.59$

$r = 0.75$
Resting State Default-Mode Network

Greicius et al., PNAS, 2003
Multiple Networks Detected with Multiple Seeds

Motor: Xiong et al., 1999

Language: Hampson et al., 2002

Executive control and Salience: Seeley et al., 2007
Multiple Networks Detected with ICA

Beckmann et al., *Philos Trans R Soc Lond*, 2005
Hypometabolism in AD

Resting PET 34 healthy subjects versus 14 AD patients.
Mild Alzheimer's Disease

Healthy Aging

Greicius et al., *PNAS*, 2004
Default-mode in healthy aging versus AD

Greicius et al., PNAS, 2004
85% sensitivity
77% specificity

Greicius et al., PNAS 2004
Reduced DMN Connectivity in PIB+ Controls

Hedden et al., J Neurosci, 2009 (also Sheline et al., Biol Psych 2010)
APOE and Connectivity in Older Controls

- Sheline et al., 2010
  E4 carriers show increases and decreases in DMN

- Machulda et al., 2011
  E4 carriers show decreases in DMN

- Westlye et al., 2011
  E4 carriers show increases in DMN

- Trachtenberg et al., 2011
  - E4 carriers show no differences in DMN (but some differences in two separate MTL networks)
APOE x Gender Interaction on AD Risk

Farrer et al, *JAMA*, 1997
ApoE x Gender Interaction

N = 131 healthy older controls

APOE, Gender, and Connectivity

Women

E4 women < E3 women

E4 men < E3 men

Dauroiseaux et al., *J Neurosci*, 2012
MCI Marching Along the Network
3 year pre-conversion  1 year pre-conversion  Conversion to AD

Whitty et al., Brain, 2007
Network-Based Neurodegeneration

Seeley et al., Neuron, 2009

Based Neurodegeneration

Syndrome-specific regional atrophy patterns: patients vs. controls.
$bvFTD \, vs \, AD = Salience \, vs \, DMN$

A  Salience Network

$bvFTD < HC$

B  Default Mode Network

$AD \, vs \, HC$

Zhou et al., *Brain*, 2010
bvFTD vs AD = Salience vs DMN

Zhou et al., *Brain*, 2010
DMN and Salience in E4 Carriers

Machulda et al., Arch Neurol, 2011
What’s New Is Old

Saper et al., Neuroscience, 1987
Conclusions

The brain is segregated into a host of distinct functional networks, detectable with resting-state fMRI.

Specific neurodegenerative disorders appear to target specific networks.

Internetwork interactions deserve attention.

Future studies:
- genetics
- plasticity
- pharmacology
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