Lecture 15: Functional Connectivity & Resting State fMRI

NOVEMBER 17, 2016

Functional Connectivity

- Functional connectivity refers to the connections between different brain regions while resting or doing a cognitive task
- Functional localization refers to the approach that brain functions are specific to regions
- Functional integration is the study of connected processes
- Can have:
  - Anatomical/structural connectivity
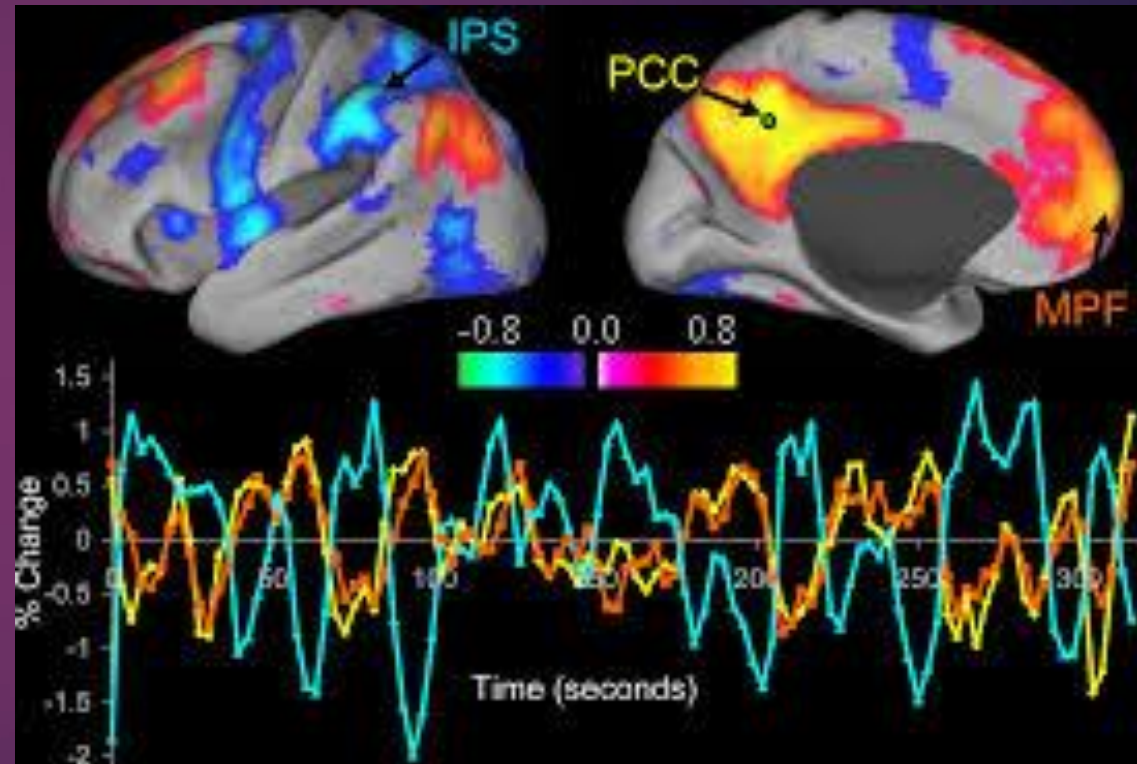 - Functional connectivity
  - Effective connectivity

Anatomical connectivity

- Connected by structures or the presence of axonal connections

- Can assess this by examining known connections or by using DTI methods
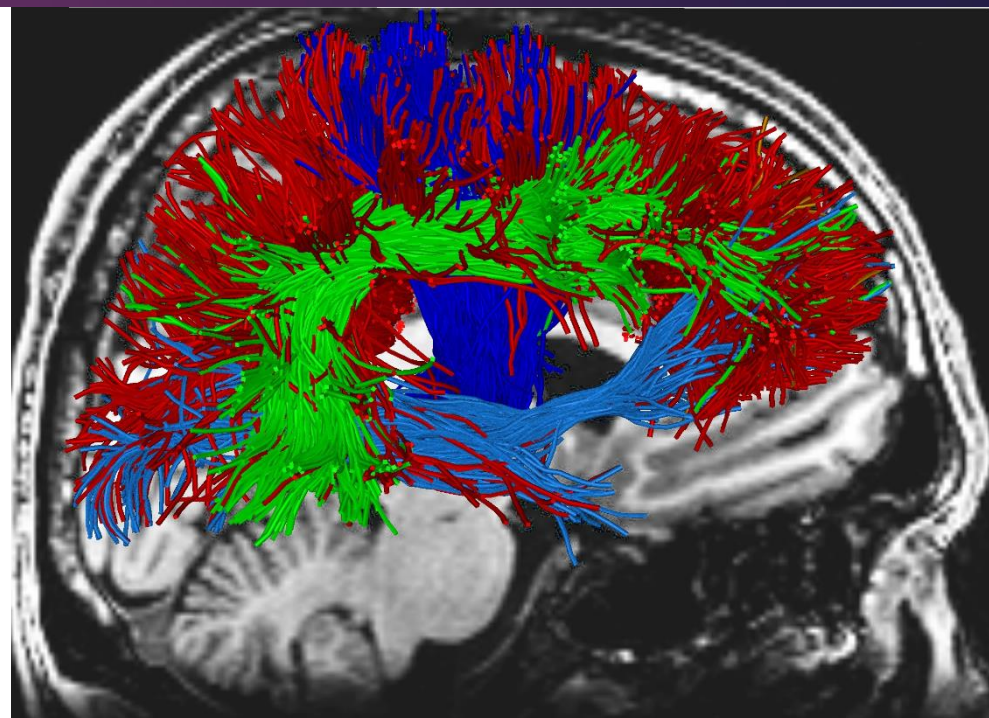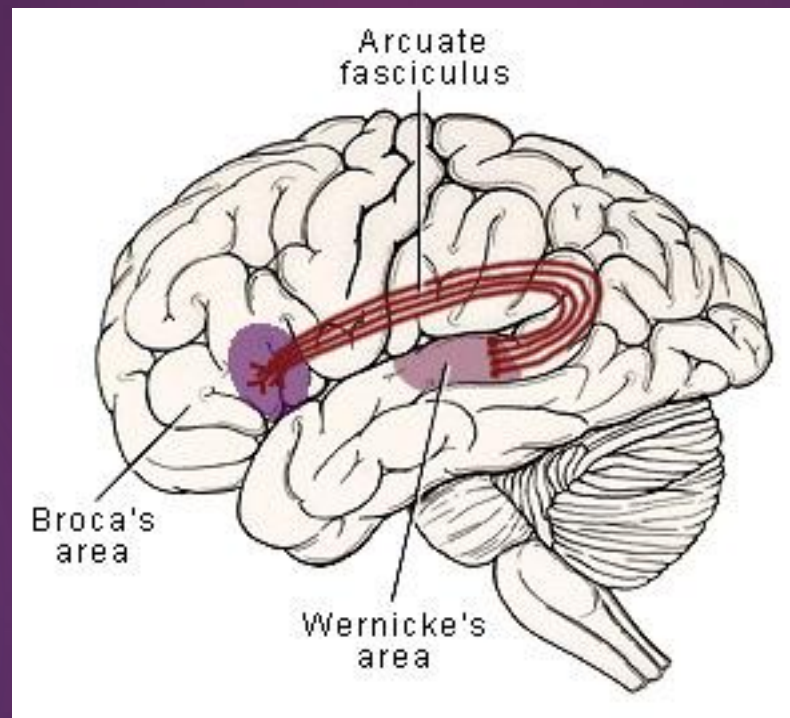
Functional Connectivity

▶ Statistical dependencies between regional time series (temporal correlations between remote neural areas)

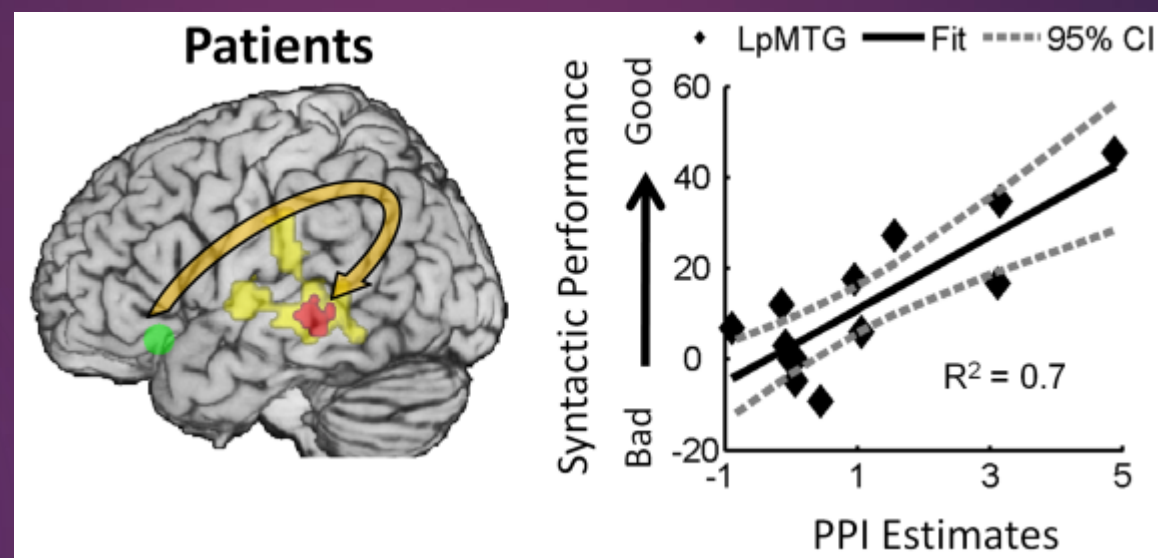▶ Can find these by picking a "seed region" and examining time correlations between this region and others

Fox & Greicius (2010) http://journal.frontiersin.org/article/10.3389/fnsys.2010.00019/full

Effective Connectivity

▶ Causal or directed influences from one region or group of neurons to another

Syntactic comprehension depends on functional interaction between frontal and temporal regions.

Rest State fMRI

- Resting state fMRI is fMRI data that is collected while an individual is not performing an explicit task

- Want to measure interactions that occur throughout the brain while "resting"

- Sort of like the "alpha" activity of EEG (relaxed, eyes closed)

- The brain areas that are temporally correlated during this resting state are called the "default mode" network of the brain
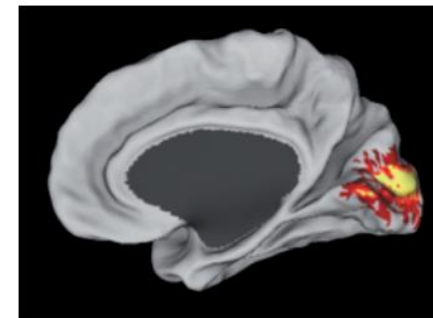
Task-evoked fMRI paradigm

▶ Bold changes from "eyes open" to "eyes closed" is apparent, but "noise" in the signal is abundant

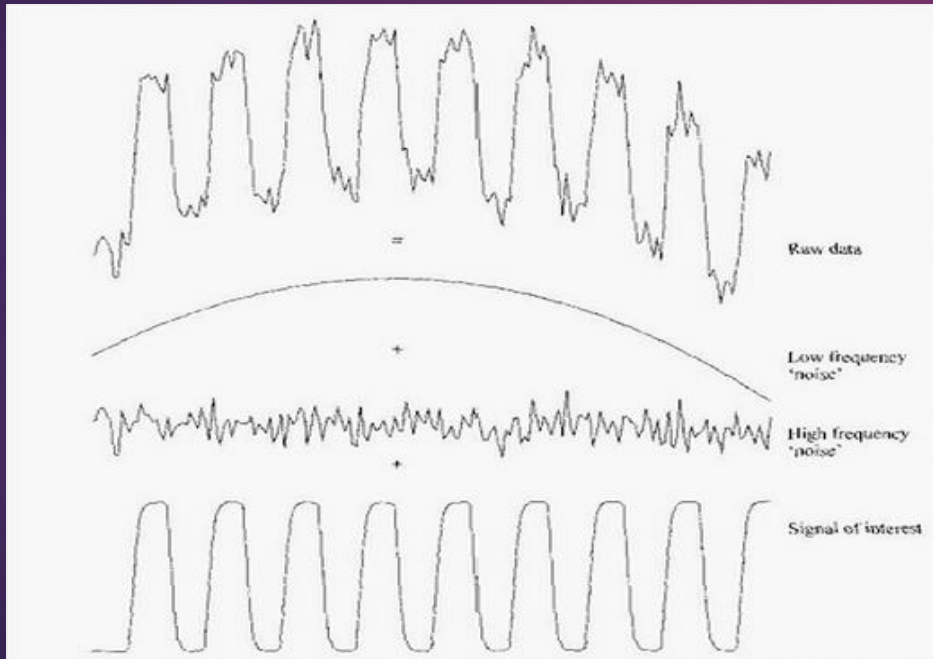▶ This signal oscillation is factored out during data modeling

Fox et al., 2007
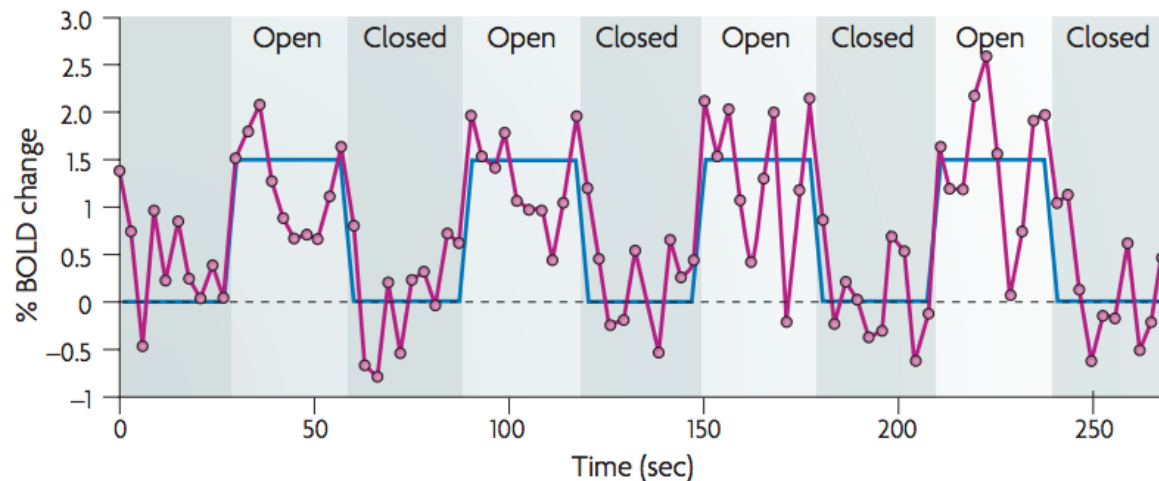
Boebinger & Knight, Introduction to Connectivity: resting-state and PPI, Methods for Dummies 2012-2013; UCL: www.fil.ion.ucl.ac.uk/.../Intro**Connectivity**

Spontaneous BOLD activity

▶ The brain is always active, even in the absence of explicit input or output

▶ Task-related changes in neuronal metabolism are only about 5% of brain's total energy consumption

▶ What is the low frequency "noise"

Mayhew et al., 1996

Spontaneous BOLD activity

Biswal et al., 1995

Van Dijk et al.,

▶ Occurs during task and at rest (intrinsic brain activity)

▶ Resting-state networks are correlation between spontaneous BOLD signals of brain regions known to be functionally and/or structurally related
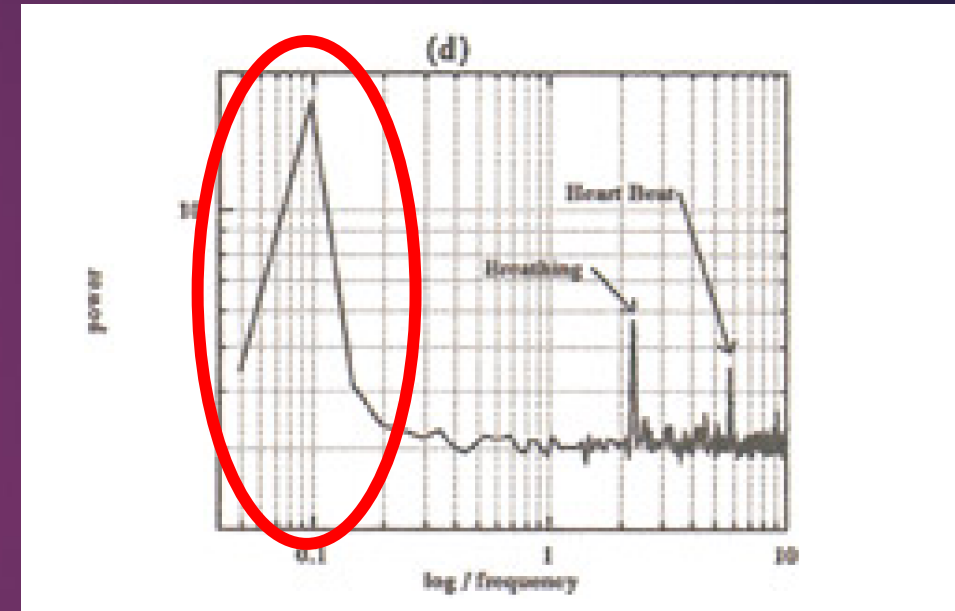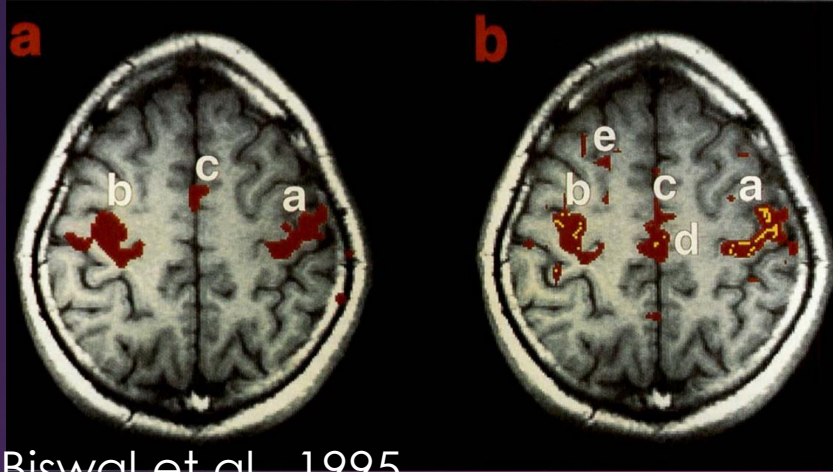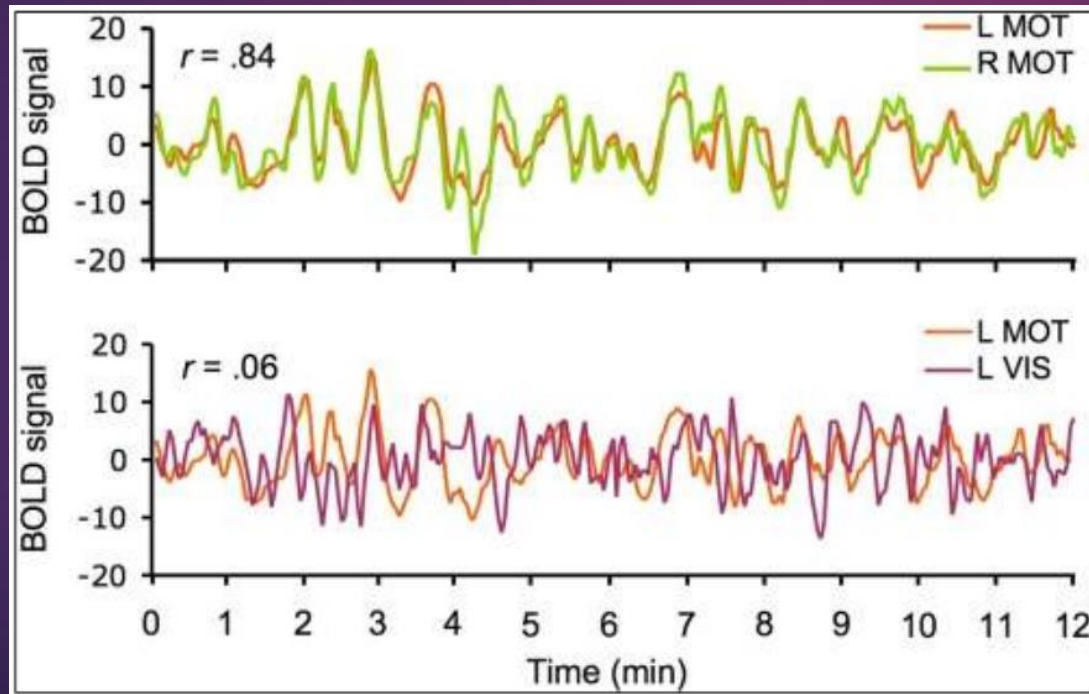
Boebinger & Knight, Introduction to Connectivity: resting-state and PPI, Methods for Dummies 2012-2013; UCL: *www.fil.ion.ucl.ac.uk/.../IntroConnectivity*

Resting-state networks (RSNs)

▶ Multiple resting-state networks (RSNs) have been found

https://www.researchgate.net/figure/280630208_fig1_Fig-1-Major-resting-state-networks-relevant-in-MDD-Representation-of-the-major
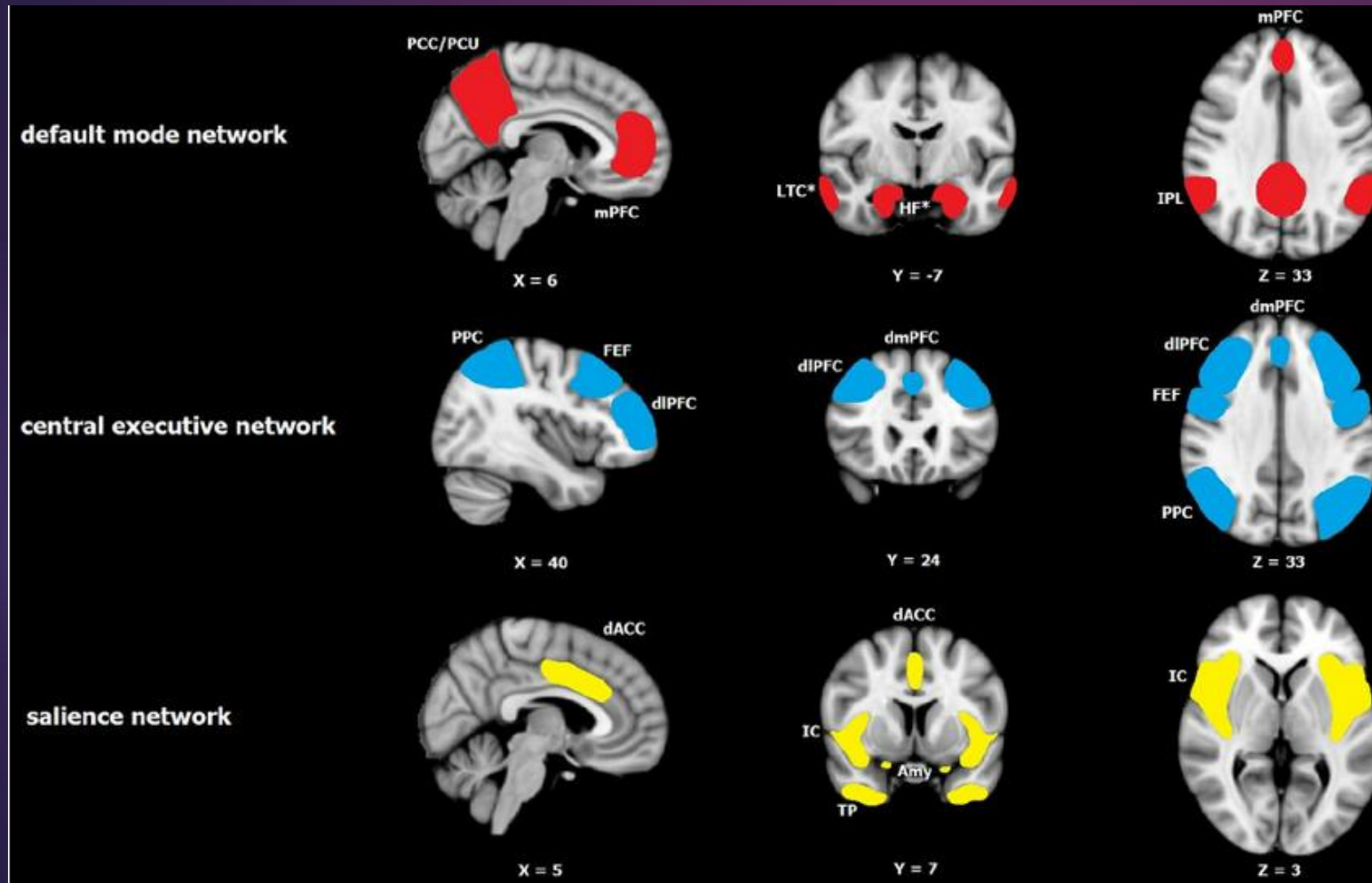
Fig. 1. Major resting-state networks relevant in MDD . Representation of the major resting-state networks relevant in MDD. The default mode network (DMN) consists of two core regions: the medial prefrontal cortex (mPFC) and the posterior cingulate cortex/precuneus (PCC/PCu), with the inferior parietal lobule (IPL) also being reported consistently. * The lateral temporal cortex (LTC) and the hippocampal formation (HF) are often found as being strongly related to the DMN, but likely constitute a subsystem within the DMN. The central executive network (CEN) is centered on the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC), and also includes the dorsomedial prefrontal cortex (dmPFC) and frontal eye fields (FEF). The salience network consists of the insular cortex (IC), dorsal anterior cingulate cortex (dACC), temporal pole (TP) and amygdala (Amy).

Default Mode Network (DMN)

► Active by default when a person is not involved in a task

► Active when a person is awake and not focused on outside world, such as daydreaming or mind-wandering

► Active when thinking of Information regarding the self:

  ► *Autobiographical information:* Memories of collection of events and facts about one's self

  ► *Self-reference:* Referring to traits and descriptions of one's self

  ► *Emotion of one's self:* Reflecting about one's own emotional state

https://en.wikipedia.org/wiki/Default_mode_network

Default Mode Network (continued)

- Thinking about others:
  - *Theory of Mind:* Thinking about the thoughts of others and what they might or might not know
  - *Emotions of other:* Understanding the emotions of other people and empathizing with their feelings
  - *Moral reasoning:* Determining just and unjust result of an action
  - *Social evaluations:* Good-bad attitude judgments about social concepts
  - *Social categories:* Reflecting on important social characteristics and status of a group

- Remembering the past and thinking about the future:
  - *Remembering the past:* Recalling events that happened in the past
  - *Imagining the future:* Envisioning events that might happen in the future
  - *Episodic memory:* Detailed memory related to specific events in time
  - *Story comprehension:* Understanding and remembering a narrative

Central Executive Network

- Brain network responsible for high-level cognitive functions, notably the control of attention and working memory

- Typically activates during fMRI tasks

- Activity in the CEN correlates with performance on executive control tasks

- Strength of within-network connectivity in the CEN is associated with higher IQ in children, adolescents, and adults

- Anticorrelated with activity in the DMN in healthy adults and may even inhibit DMN under certain circumstances

http://www.sciencedirect.com/science/article/pii/S187892931400053X

http://www.iapsych.com/articles/bressler2010.pdf

Salience Network

- Network that attends to the importance of matters
- Selects things out of the environment that are 'salient'
  - Notable or stand out
  - Meaningful in some way
  - Behaviorally relevant

- Regulates changes in other networks
- Thought to mediate our response to important internal or external signals

Resting-state fMRI: acquisition

- Resting-state paradigm
  - no task; participant asked to lie still
  - time course of spontaneous BOLD response measured
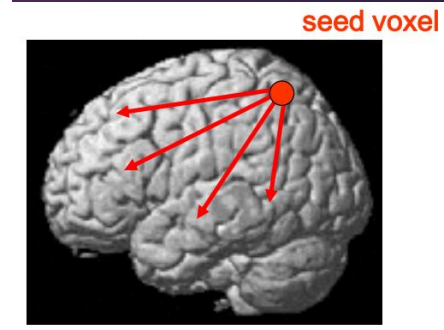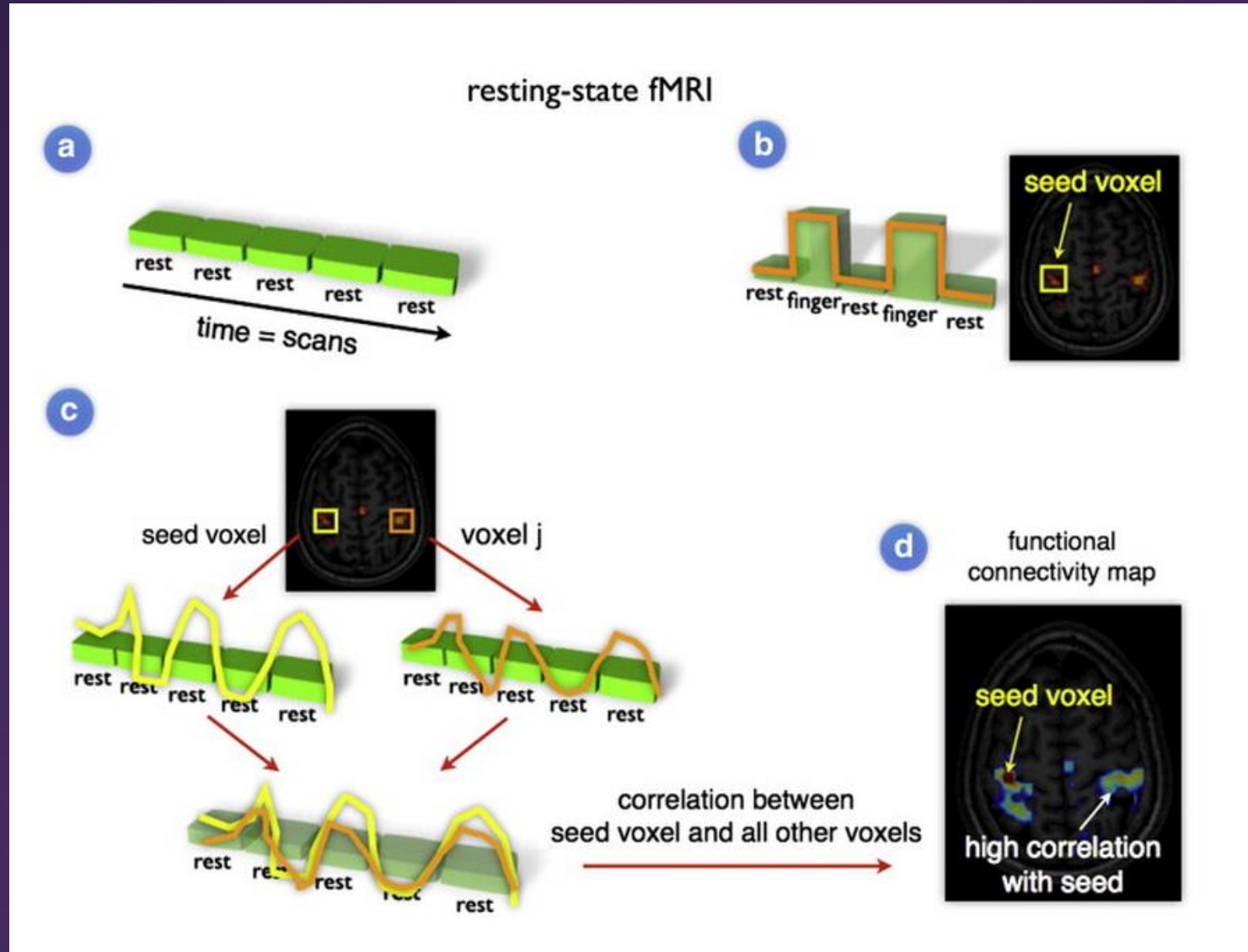- Less susceptible to task-related confounds
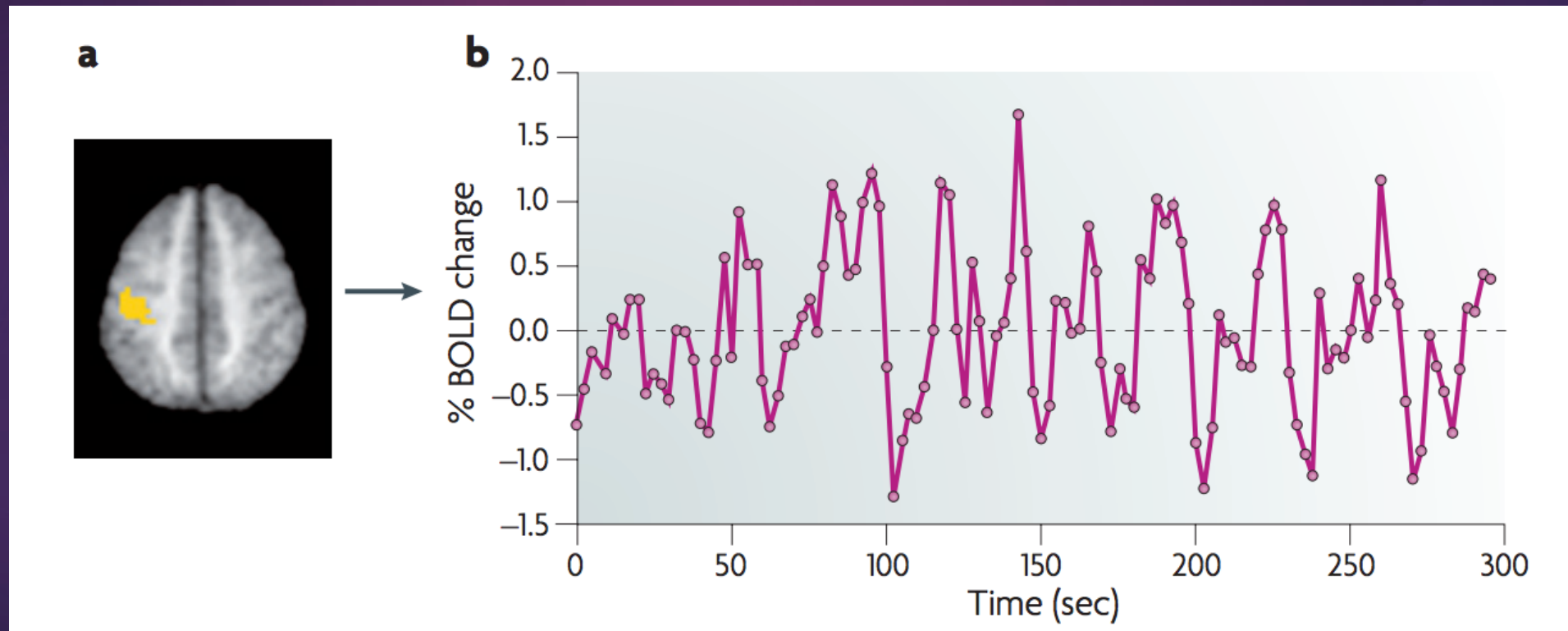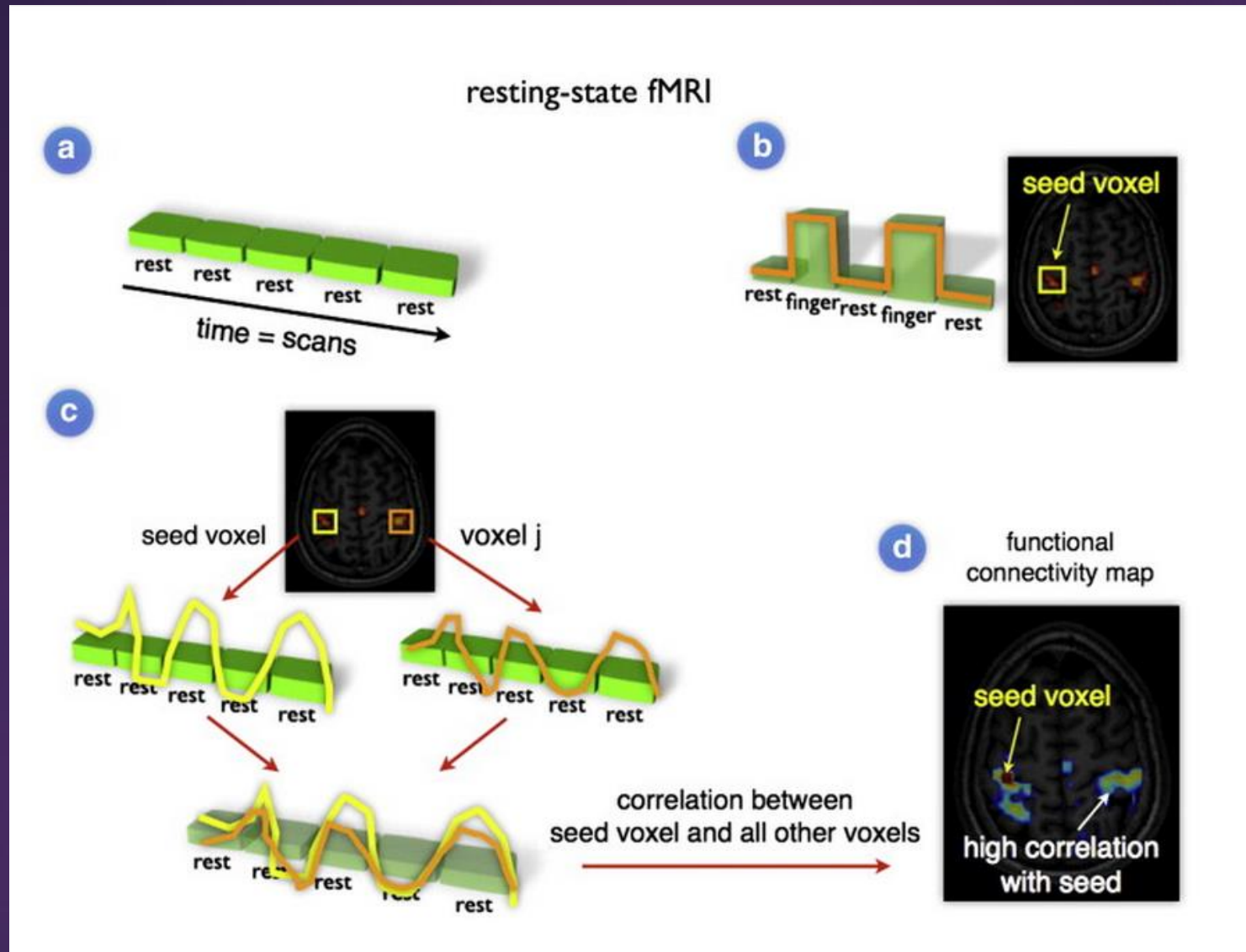

Fox & Raichle, 2007

& Hulshoff Pol, 2010

resting-state fMRI

Marreiros, 2012
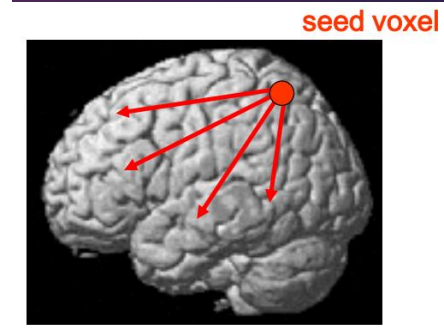
▶ model-dependent methods: seed method

  ▶ *a priori* or hypothesis-driven from previous literature
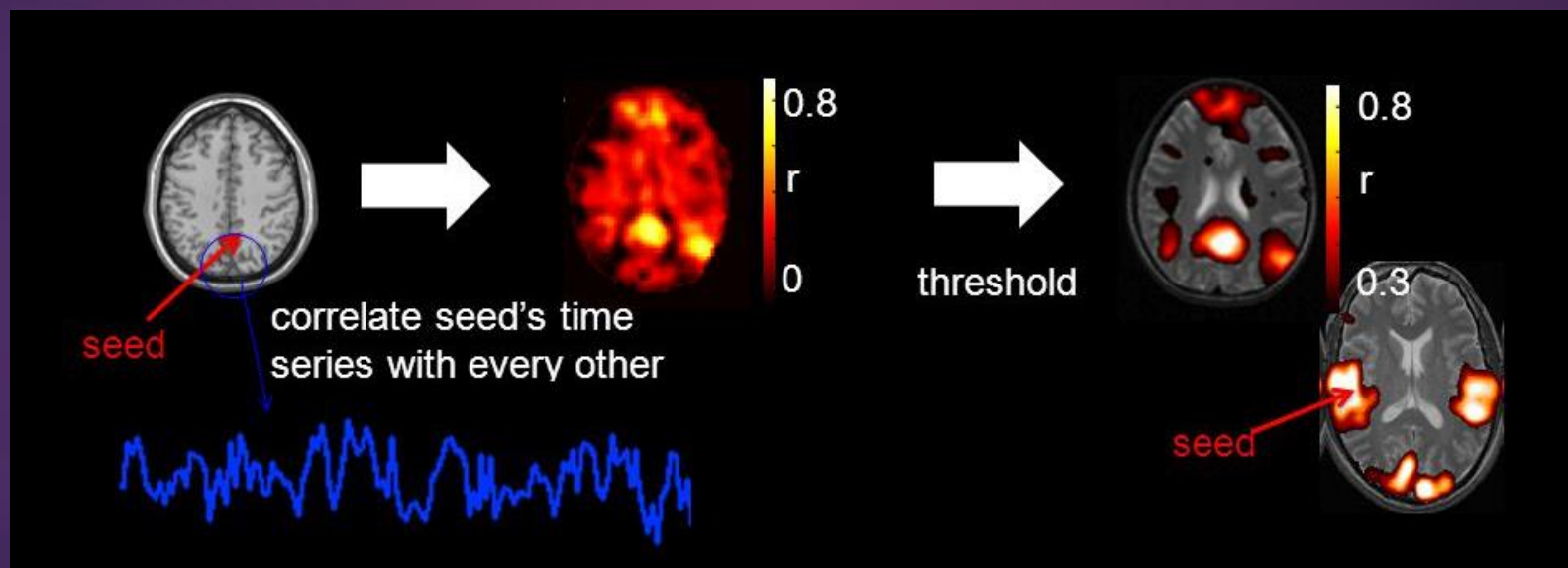
resting-state fMRI

Marreiros, 2012

- ▶ model-dependent methods: seed method
  - ▶ *a priori* or hypothesis-driven from previous literature

van den Heuvel & Hulshoff Pol, 2010

Functional Connectivity Analysis

- Pick a seed region

- Correlate the time series of this "seed" with the time series of all other voxels

More Functional Networks

- Black dots indicate seed regions

- Computed from 1000 subjects

- More detailed analysis reveals that these networks can be broken down even further into smaller networks

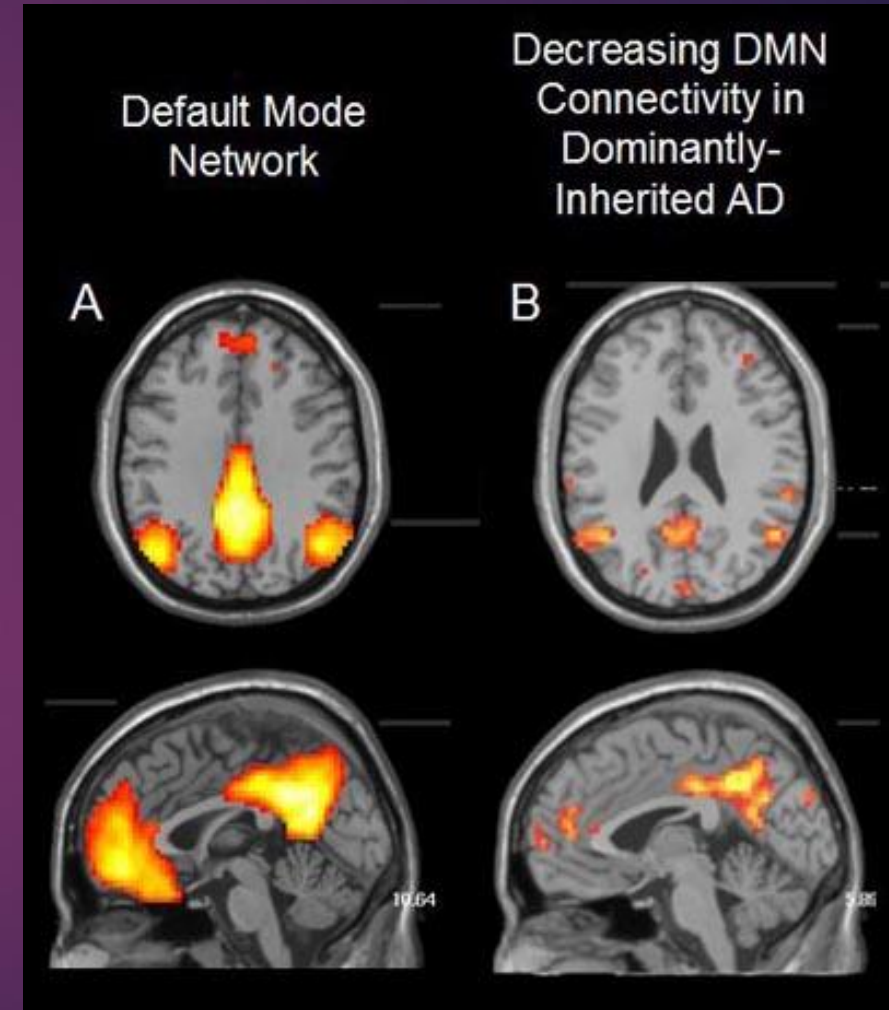http://www.nature.com/neuro/journal/v16/n7/full/nn.3423.html#supplementary-information
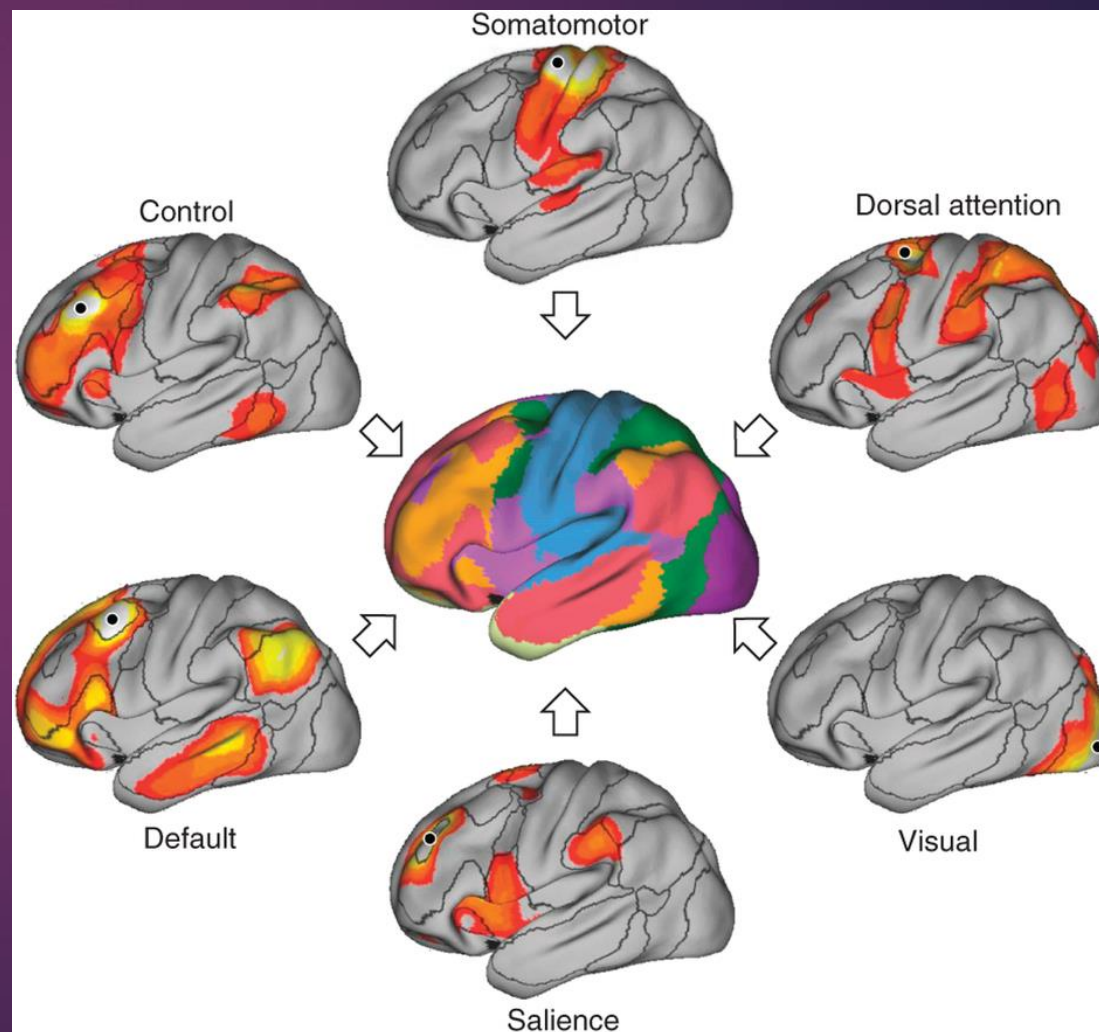
Research Applications

▶ Examine differences in connectivity in patient populations vs controls

ADHD	(Zhu et al., 2005, 2008; Cao et al., 2006; Tian et al., 2006; Zang et al., 2007; Castellanos et al., 2008; Wang et al., 2009)	Variable: reduced connectivity within the DMN, reduced anticorrelations with the DMN, increased connectivity in the salience network
Healthy aging	(Andrews-Hanna et al., 2007; Damoiseaux et al., 2008)	Decreased correlations within the DMN
Alzheimer's	(Li et al., 2002; Greicius et al., 2004; Wang et al., 2006a,b, 2007; Allen et al., 2007; Supekar et al., 2008)	Decreased correlations within the DMN including hippocampi, decreased anticorrelations with the DMN, and reduced local connectivity as reflected in clustering coefficients

Functional Connectivity in Inherited Alzheimer's Disease (AD)

- **Early-onset, autosomal dominant AD** is a form of AD that develops before the age of 65.

- The early-onset, autosomal dominant form of AD is caused by changes (mutations) one of three different genes: *APP*, *PSEN1*, and *PSEN2*. The condition is inherited in an autosomal dominant manner.

- Adults with autosomal dominant AD mutations show decreased connectivity throughout the default-mode network (DMN) relative to non-mutation carriers, as revealed by functional magnetic resonance imaging (fMRI) brain scans.

https://rarediseases.info.nih.gov/diseases/12798/early-onset-autosomal-dominant-alzheimer-disease
http://www.alzforum.org/news/conference-coverage/big-picture-familial-ads-biomarker-data-resemble-load

In Summary

- Functional connectivity of fMRI can be used to show regions that work together in the brain

- These regions may not necessarily be connected anatomically

- Several connectivity networks exist and more are being found all the time

- Default mode network is the most popular

- Connectivity analysis can be used to examine neurological disorders in hopes of understanding what the underlying mechanisms of the disease