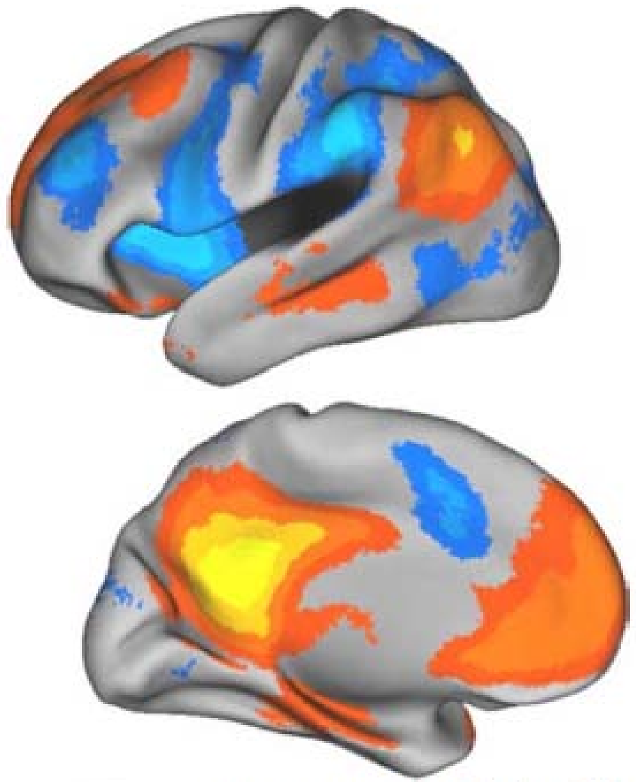
Resting-State functional Connectivity MRI (fcMRI)

NeuroImaging

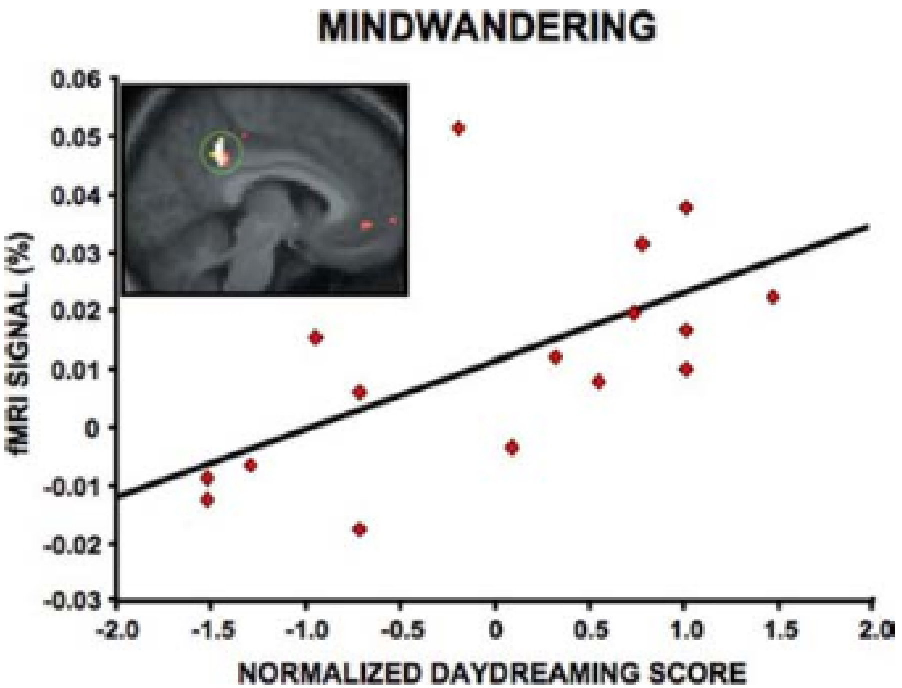
ANTICORRELATIONS



Intrinsic activity suggests that the default network is negatively correlated (anticorrelated) with brain systems that are used for focused external visual attention. Anticorrelated networks are displayed by plotting those regions that negatively correlate with the default network (shown in blue) in addition to those that positively correlate (shown in red). These two anticorrelated networks may participate in distinct functions that compete with one another for control of information processing within the brain.

Randy L. Buckner et. at., The Brain's Default Network: Anatomy, Function, and Relevance to Disease, Ann. N. Y. Acad. Sci. 1124: 1-38 (2008)

Interesting Facts



. The default network is most active in individuals who report frequent mindwandering, suggesting a functional role in spontaneous cognition. Activity estimates are plotted for 16 subjects from PCC/Rsp (region shown in insert) from a task contrast conducive to encouraging mindwandering. The activity within this region is significantly correlated with individual self-reports of daydreaming obtained outside the scanner. Adapted from data published in Mason et al. (2007).

- human brain is 2% of total body mass but consumes 20% of total energy, most to support ongoing neuronal signaling
- task driven neuronal metabolism is relatively small, <5%, compared to resting-state consumption

See references at the back of this PowerPoint

Background/Rationale

- Brain is very active even w/o external stimulus. (resting-state fMRI acquisition: eyes closed but remain awake; 10-15 minutes)
- With BOLD signal, at rest, fcMRI time series (< 0.1 Hz) reflects spontaneous neuronal activity, which shows strong coherence both in resting state and during a visual stimulation; connectivity is consistent
- fcMRI is widely used to study brain networks that exhibit correlation (both positive and negative), identified brain network during resting state is called resting-state networks (RSNs)
- Run structure, temporal or spatial resolution only slightly affects fcMRI
- Connectivity result is consistent within and among healthy subjects

See references at the back of this PowerPoint

Spontaneous BOLD signal

- Resting State signal was viewed as “noise” in task-oriented studies, it was subtracted or averaged out through various techniques
- It is not random noise, but structurally and reliably organized
- Not a direct measure of neuronal activity, but reflects de-oxyhaemoglobin concentration (blood flow, volume and metabolism)

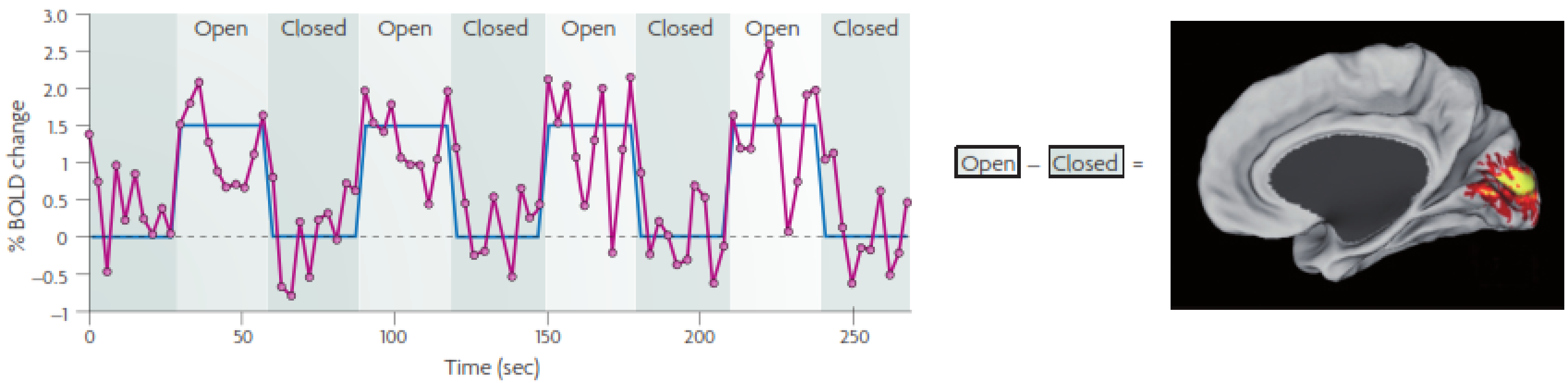


Figure 1 | **Traditional fMRI analysis and BOLD noise.** Unaveraged blood oxygen level dependent (BOLD) time course (magenta) from a region in the primary visual cortex during a simple task paradigm that requires subjects to open and close their eyes. The paradigm is shown in blue (delayed to account for the haemodynamic response). Traditional functional magnetic resonance imaging (fMRI) analysis involves correlating BOLD data with a stimulation time-course across multiple blocks. This in effect averages across each condition and performs a subtraction, minimizing ‘noise’ in the BOLD signal and highlighting regions that are modulated by the task paradigm. In this case, subtraction of the eyes-closed condition from the eyes-open condition identifies a BOLD signal intensity difference in the primary visual cortex (shown on the right).

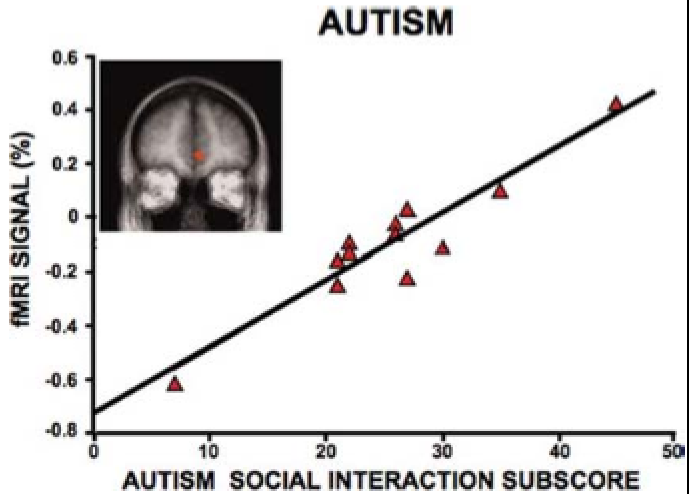
Michael D. Fox et al., Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging, Nature, Sept 2007, vol 8

Clinical Applications

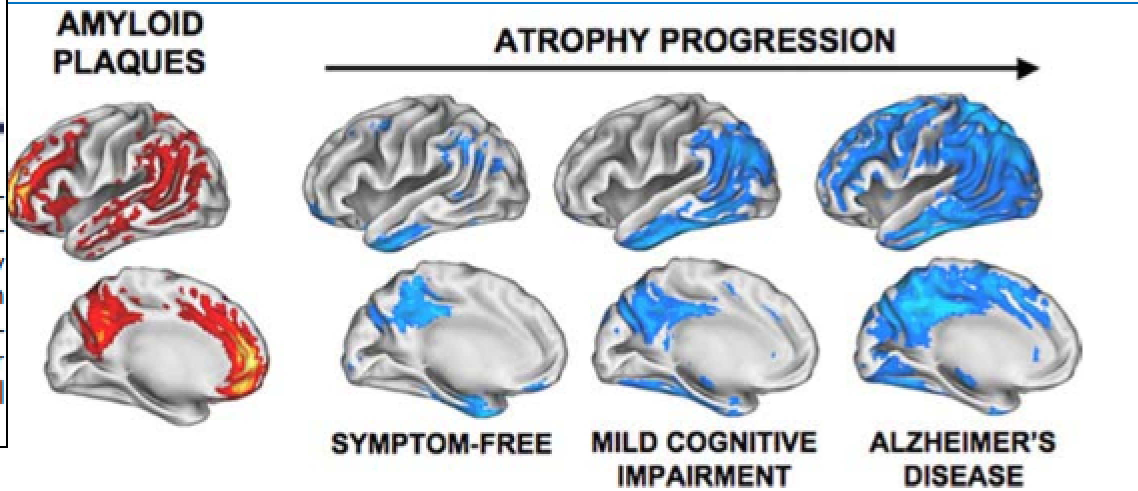
- A potential diagnostic tool to detect neurological and psychiatric disorder via strength of correction or when it changes or absent
  - correlation disturbances of resting state signal can imply pathological states like Alzheimer's, depression, schizophrenia, autism, epilepsy...
  - Correlation changes can indicate brain maturation, altered states of consciousness, measure of development, pharmacological manipulation or anesthesia
- Presurgical planning
  - To replace more invasive pre-surgical mapping
  - To allow pre-surgical mapping while subjects are at rest or slightly medicated
  - To maximize the size of tumor removal or brain tissue resection while minimizing the harm to language function in eloquent cortex.

See references at the back of this PowerPoint

Clinical Implication



Default network activity tracks the severity of social dysfunction in autism. An exploratory correlational analysis by Kennedy et al. (2006) found that activity within MPFC (region shown in inset) was correlated with social impairment as measured by the Autism Diagnostic Interview–Revised. Individuals with autism spectrum disorder who showed less task-induced deactivation had lower social impairment scores. Adapted from Kennedy et al. (2006).



Alzheimer's disease may be causally related to default network activity. Regions manifesting default activity in young adults (e.g., FIGS. 2 and 7) are highly similar to those that show pathology in early stages of the disease as measured by molecular imaging of amyloid plaques using PET (left). These regions, in turn, appear affected by structural atrophy as measured by longitudinal MRI (right). One possibility is that activity within the default network augments an activity-dependent or metabolism-dependent cascade that leads to the formation of Alzheimer's disease pathology. Adapted from Buckner et al. (2005).

Randy L. Buckner et. at., The Brain's Default Network: Anatomy, Function, and Relevance to Disease, Ann. N. Y. Acad. Sci. 1124: 1-38 (2008)

Low-frequency Spontaneous Fluctuations in BOLD signal

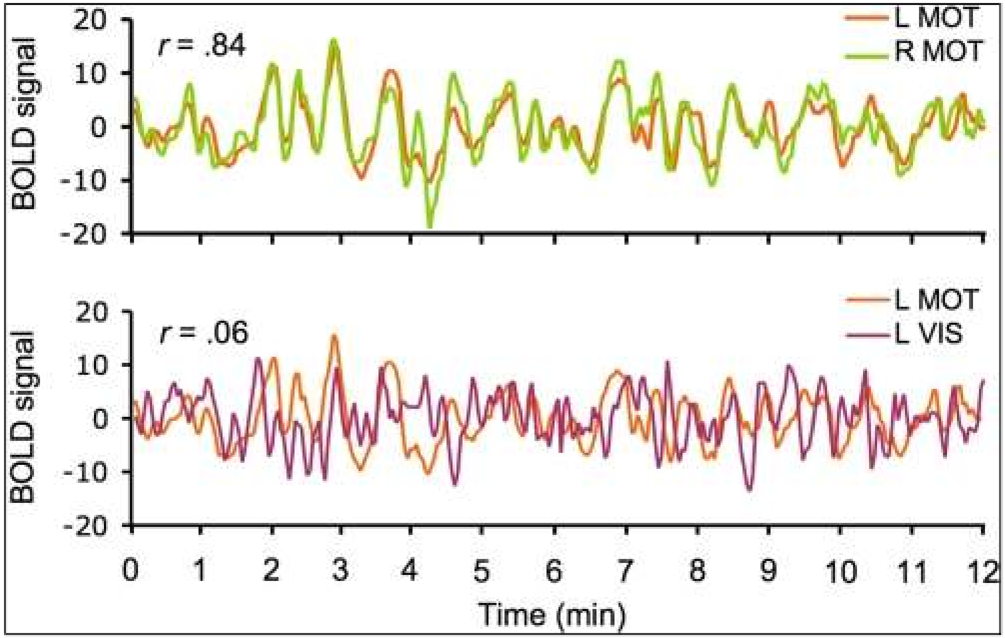


Fig. 1.

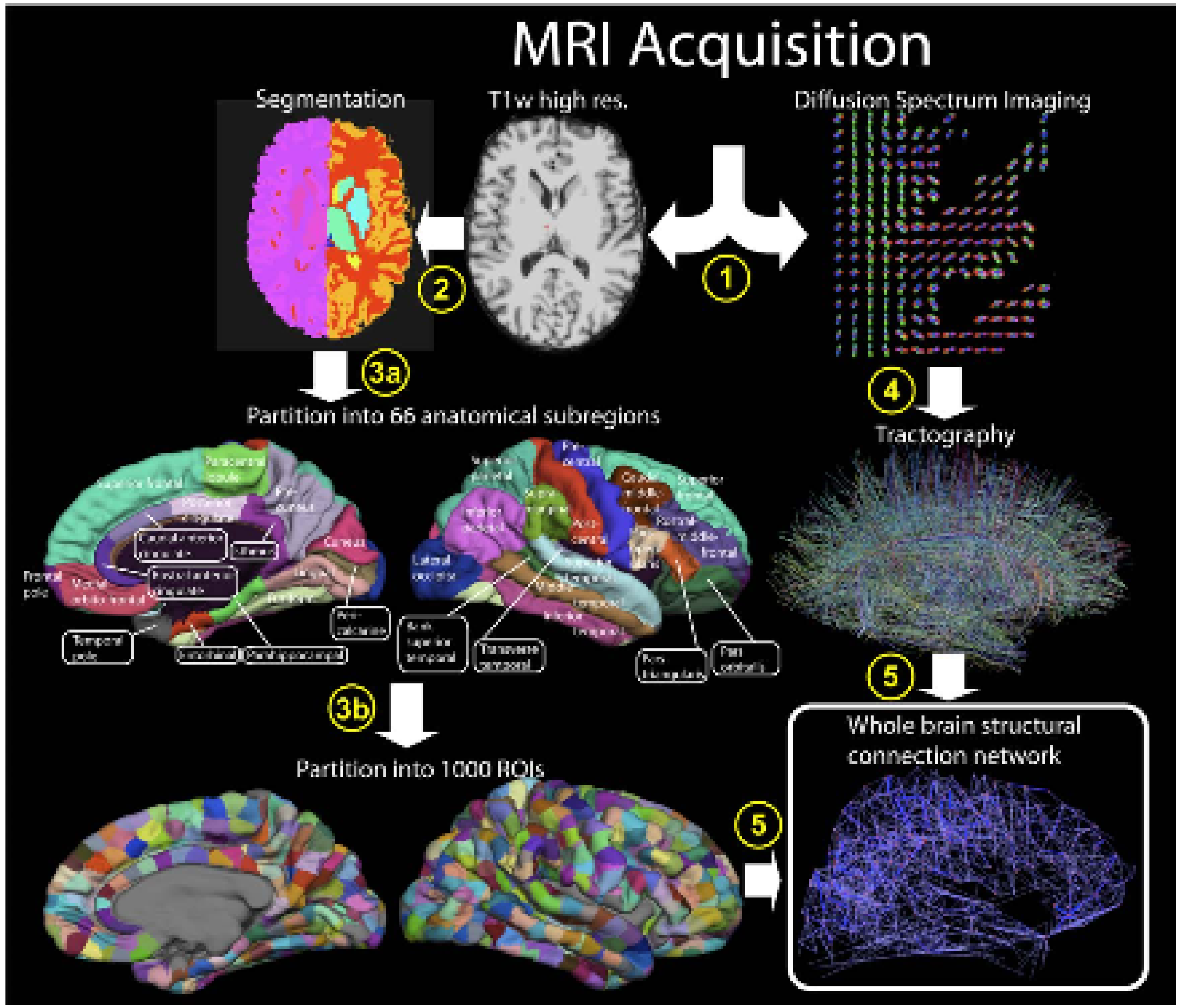
The basis of functional connectivity MRI (fcMRI). Low-frequency spontaneous fluctuations in the blood-oxygenation-level-dependent (BOLD) signal are correlated over time between regions within the same brain systems. Examples from a single subject depict correlated spontaneous fluctuations between left and right motor cortex (*top*) and the absence of correlation between motor and visual regions (*bottom*). fcMRI methods make use of the selective correlations between regions to map the organization of brain systems. L, left; R, right; MOT, motor cortex; VIS, visual cortex.

Koene R. A. Van Dijk et al., Intrinsic Functional Connectivity As a Tool For Human Connections: Theory, Properties, and Optimization, J Neurophysiol 2010 January; 103 (1): 297 - 321

MRI techniques for invasive brain connectivity mapping

- In the past, majority are inferences from invasive tracing techniques of non-human primates and postmortem in humans (limited to connections spanning in short distances)
- Noninvasive fMRI has become popular and mainstay
- Noninvasive mapping using MRI techniques include:
  - Methods based on functional correlations like fcMRI
    1. Earlier approaches were on stimulus-evoked
    2. In 1995, Biswal et al., observed intrinsic, passive activities while subjects at rest
  - diffusion-based methods like diffusion tensor imaging (DTI)
  - High angular resolution diffusion imaging (HARDI)
  - Distant effect based measurement like neural stimulation
  - They all present strength and shortcomings in the technique/methods

Koene R. A. Van Dijk et al., Intrinsic Functional Connectivity As a Tool For Human Connections: Theory, Properties, and Optimization, J Neurophysiol 2010 January; 103 (1): 297 - 321



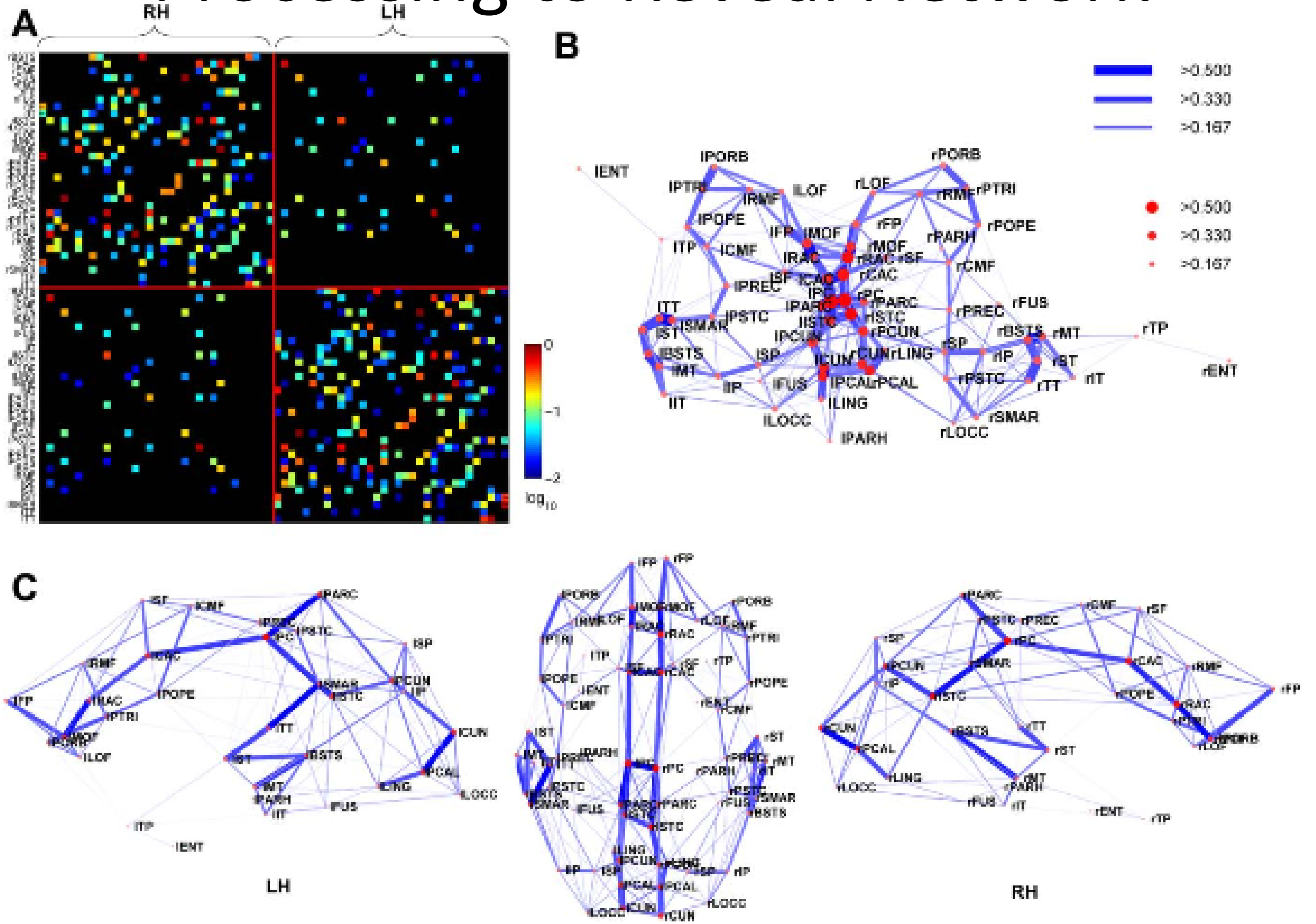
. Extraction of a Whole Brain Structural Connectivity Network

(1) High-resolution T1 weighted and diffusion spectrum MRI (DSI) is acquired. DSI is represented with a zoom on the axial slice of the reconstructed diffusion map, showing an orientation distribution function at each position represented by a deformed sphere whose radius codes for diffusion intensity. Blue codes for the head-feet, red for left-right, and green for anterior-posterior orientations. (2) White and gray matter segmentation is performed from the T1-weighted image. (3a) 66 cortical regions with clear anatomical landmarks are created and then (3b) individually subdivided into small regions of interest (ROIs) resulting in 998 ROIs. (4) Whole brain tractography is performed providing an estimate of axonal trajectories across the entire white matter. (5) ROIs identified in step (3b) are combined with result of step (4) in order to compute the connection weight between each pair of ROIs. The result is a weighted network of structural connectivity across the entire brain. In the paper, the 66 cortical regions are labeled as follows: each label consists of two parts, a prefix for the cortical hemisphere (r = right hemisphere, l = left hemisphere) and one of 33 designators: BSTS = bank of the superior temporal sulcus, CAC = caudal anterior cingulate cortex, CMF = caudal middle frontal cortex, CUN = cuneus, ENT = entorhinal cortex, FP = frontal pole, FUS = fusiform gyrus, IP = inferior parietal cortex, IT = inferior temporal cortex, ISTC = isthmus of the cingulate cortex, LOCC = lateral occipital cortex, LOF = lateral orbitofrontal cortex, LING = lingual gyrus, MOF = medial orbitofrontal cortex, MT = middle temporal cortex, PARC = paracentral lobule, PARH = parahippocampal cortex, POPE = pars opercularis, PORB = pars orbitalis, PTRI = pars triangularis, PCAL = pericalcarine cortex, PSTS = postcentral gyrus, PC = posterior cingulate cortex, PREC = precentral gyrus, PCUN = precuneus, RAC = rostral anterior cingulate cortex, RMF = rostral middle frontal cortex, SF = superior frontal cortex, SP = superior parietal cortex, ST = superior temporal cortex, SMAR = supramarginal gyrus, TP = temporal pole, and TT = transverse temporal cortex.

doi:10.1371/journal.pbio.0060159.g001

Patric Hagmann et. at., Mapping the Structural Core of Human Cerebral Cortex, PLoS Biology, July 2008, Vol 6 Issue 7 e159

Processing to Reveal Network



Average Regional Connection Matrix, Network Layout, and Connectivity Backbone

(A) Matrix of inter-regional fiber densities between pairs of anatomical subregions, obtained by averaging over fiber densities for all pairs of ROIs within the regions, and averaging across all five participants. Connection weights are symmetric and are plotted on a logarithmic scale. For corresponding plots for all individual participants, see Figure S2.

(B) Network layout.

(C) Dorsal and medial views of the connectivity backbone in anatomical coordinates.

doi:10.1371/journal.pbio.0060159.g004

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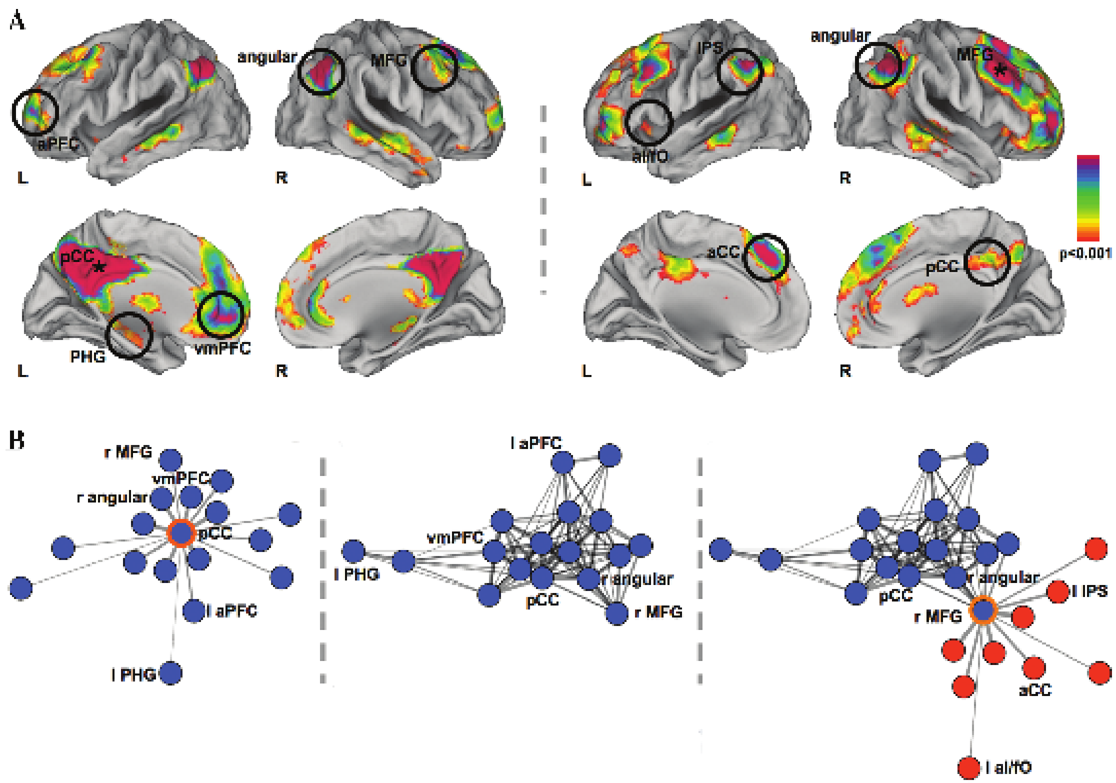
Overall Interests and Concerns

- Physiological noise; particularly the variation over time in breathing rate (~0.03Hz); filter can't remove (or completely)
- Interest in negative correlation is emerging
  - Robust only if whole-brain signal regression is applied
  - The most compelling proof for antagonistic relationships
  - To under the neurophysiological origins outside BOLD
- Graph Theory – hub of the connection, not just strength (see next slide)
- Imaging Acquisition techniques are reliable and better understood now
- Pre-processing is important and so is post-processing for trade-off
- Acquisition parameters can affect results, but only slightly
- Two major networks – default network and dorsal attention system
  - Each has multi, bilateral regions; show both pos and neg correction

See references at the back of this PowerPoint

Graph Theory – emerging research

- Position – likely will mischaracterize brain network structure and function if graph theory is not considered
- Focus on analysis of rs-fcMRI corrections
- Goal – to quantify the existence and strength of functional relationships between regions, the hub



Gagan S. Wig, Concepts and Principles in the analysis of brain networks, Ann. N. Y Academy of Sc. ISSN 0077-8923

Imaging limitations and Opportunities

- Even more rapid acquisition of large-scale data set
- Resolution limit of imaging tool constraint brain network analysis to nodes only above the millimeter scale
- Need to accurately identify boundaries on each unique region, based on patterns of connectivity or clustering
- Not just imaging, but visualization methods: from pairwise relations to understand the brain at large-scale complexity
- Simulation and/or image-guide navigation using already collected fMRI data (see next slide for example)

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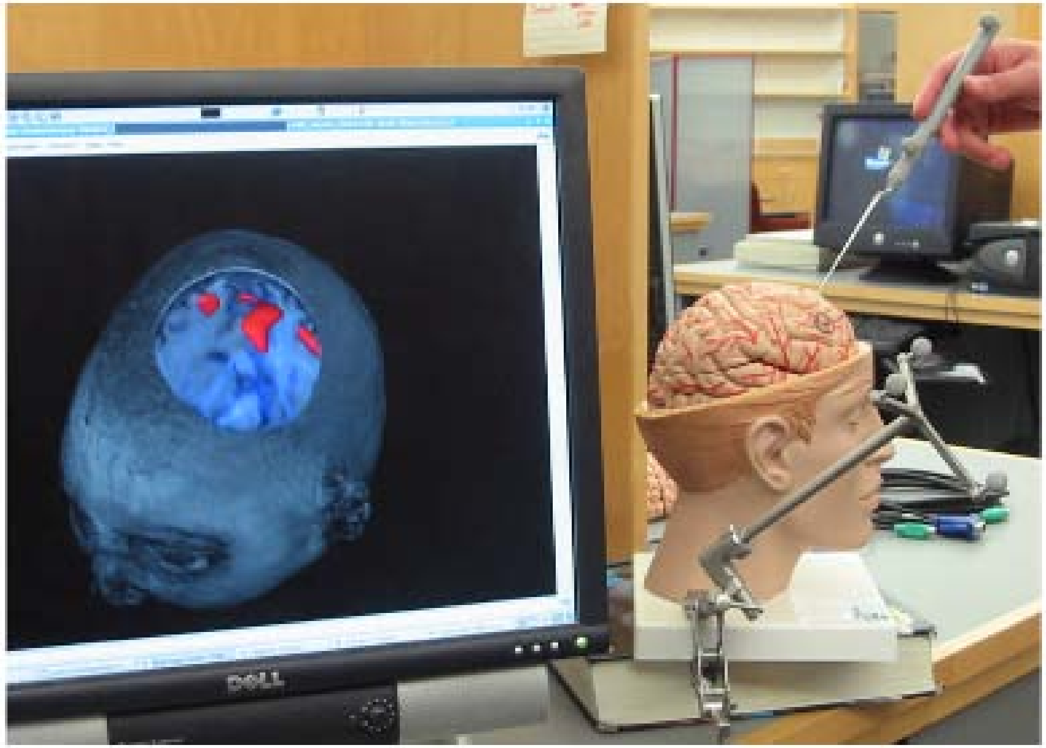
Image-guided navigation with already collected fMRI data



A photograph of our 3D mock operating room setup being used with the VVCranial system to perform image-guided navigation in the patient data. On the right you can see a rubber brain that is registered with the actual patient data which is being displayed on the screen. The probe, in the hand of the user in the photograph, is being tracked by the stereo infrared cameras and its coordinates are communicated realtime to our system. Based on the position and selected cropping shape, the user can interact with the data (see attached video).

Alark Joshi et. at., Novel Interaction Techniques for Neurosurgical Planning and Stereotactic Navigation, IEEE Trans Vis Comput Graph. 2008; 14(6) 1587-1594. doi: 10.1109/TVCG. 2008.150

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