Current issues in data-intensive brain-related research—a scan of the research landscape

- *For Spring 2016, the focus areas for funding are:*
  - *Projects involving collection of new brain imaging data*
  - *Big data approaches to neuroscience (using existing or new data)*
  - *Integration of multimodal data to bridge spatial and temporal scales*
  - *The use of brain imaging to provide individualized predictions*
  - *Novel models for capturing brain dynamics*
  - *Scalable informatics approaches for processing or sharing*

Some outstanding questions

- **1. Prediction: using neuroscience to predict peoples' fate or actions.**
- **2. Mind reading: using neuroscience as a lie detector or to see emotional states.**
- **3. Responsibility: using neuroscience to determine whether people have free will.**
- **4. Treatment: using neuroscience in medical care.**
- **5. Enhancement: using neuroscience to juice our capabilities.**

Yet another view

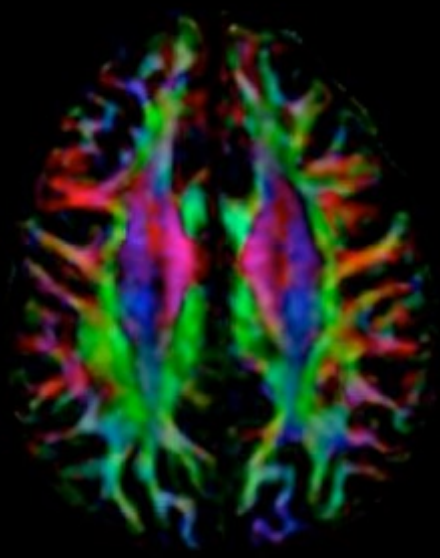
- 1. How does the brain generate consciousness?
- 2. What are the limits of human life and physiology?
- 3. Can we replace damaged brain parts with computational devices?
- 4. What happens when you die?
- 5. What are the cures for the world's biggest health problems, like cancer, heart disease and dementia?
- 6. Will we ever reconcile the nature versus nurture debate?
- 7. Is ageing inevitable?
- 8. Will we ever be able to predict the future of economic, political and other social systems?
- 9. What is life?
- 10. How can we put evidence into practice perfectly, in medicine: harnessing all the data we have on our patients, and meshing it with all the research data, for the best care?
- 11. Is there a limit to how smart individuals and communities can be?
- 12. What are the possibilities for lab-grown fish and could this provide a counter to our overexploitation of the oceans?
- 13. What makes us "human", and will we ever find out?
- 14. Is biology as universal as chemistry and physics?
- 15. How are bodies able to repair themselves?
- 16. How does the genome allow a brain to develop that has inborn talents and tendencies – if we have an inborn fear of say, snakes, how does that get wired up in a brain?
- 17. Why have humans evolved music?
- 18. Are we alone? Is there life in space, and if so, how is it similar or different than life here on Earth?
- 19. Does the universe have purpose and meaning?
- 20. How does the brain work and can we fix it when it goes wrong?
- 21. Is suspended animation possible for humans?
- 22. Can we look forward to sustainably supporting a stable human population on this planet, and how can we protect biodiversity at the same time?
- 24 Big Questions Science Still Needs To Answer
- 23. Is sexuality genetic?
- 24. What question has not yet been formulated by anyone?

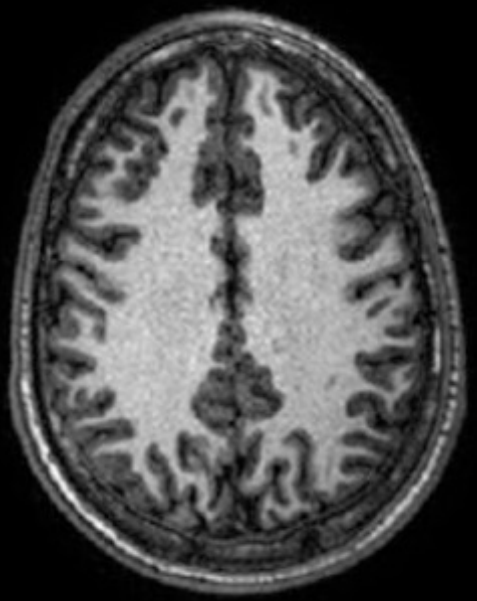
Another view on outstanding questions

- Consciousness: What is the neural basis of subjective experience, cognition, wakefulness, alertness, arousal, and attention? Is there a "hard problem of consciousness"? If so, how is it solved? What, if any, is the function of consciousness?[1][2]
- Perception: How does the brain transfer sensory information into coherent, private percepts? What are the rules by which perception is organized? What are the features/objects that constitute our perceptual experience of internal and external events? How are the senses integrated? What is the relationship between subjective experience and the physical world?
- Learning and memory: Where do our memories get stored and how are they retrieved again? How can learning be improved? What is the difference between explicit and implicit memories? What molecule is responsible for synaptic tagging?
- Neuroplasticity: How plastic is the mature brain?
- Development and evolution: How and why did the brain evolve? What are the molecular determinants of individual brain development?
- Free will, particularly the neuroscience of free will
- Sleep: What is the biological function of sleep? Why do we dream? What are the underlying brain mechanisms? What is its relation to anesthesia?
- Cognition and decisions: How and where does the brain evaluate reward value and effort (cost) to modulate behavior? How does previous experience alter perception and behavior? What are the genetic and environmental contributions to brain function?
- Language: How is it implemented neurally? What is the basis of semantic meaning?
- Diseases: What are the neural bases (causes) of mental diseases like psychotic disorders (e.g. mania, schizophrenia), Parkinson's disease, Alzheimer's disease, or addiction? Is it possible to recover loss of sensory or motor function?
- Movement: How can we move so controllably, even though the motor nerve impulses seem haphazard and unpredictable? [3]
- Computational theory of mind: What are the limits of understanding thinking as a form of computing?
- Computational neuroscience: How important is the precise timing of action potentials for information processing in the neocortex? Is there a canonical computation performed by cortical columns? How is information in the brain processed by the collective dynamics of large neuronal circuits? What level of simplification is suitable for a description of information processing in the brain? What is the neural code?

Brain Imaging

- MRI data
  - fMRI
  - sMRI
  - dMRI
  - MRS
- MEG/EEG
- Task vs Rest
- Connectivity (Functional/Effective)

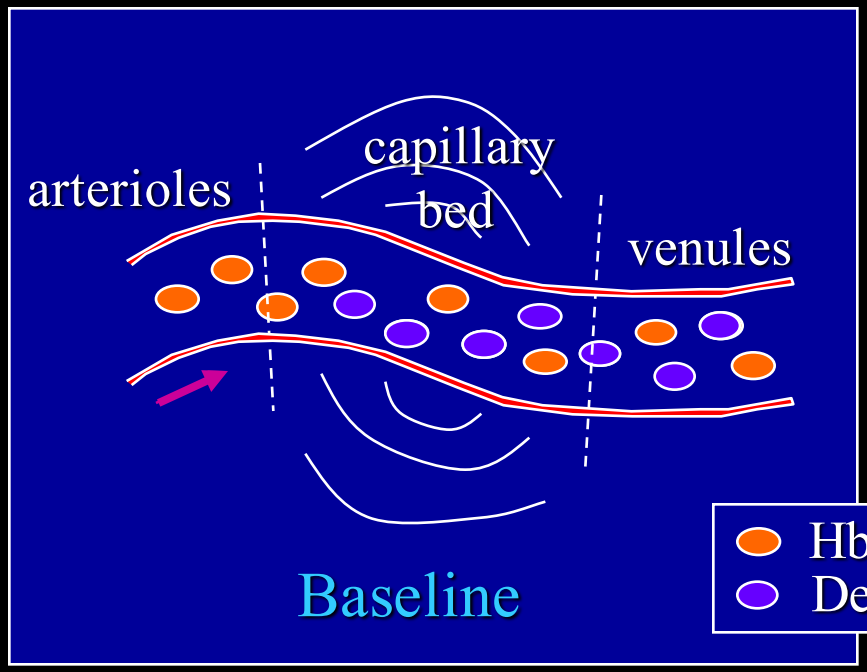


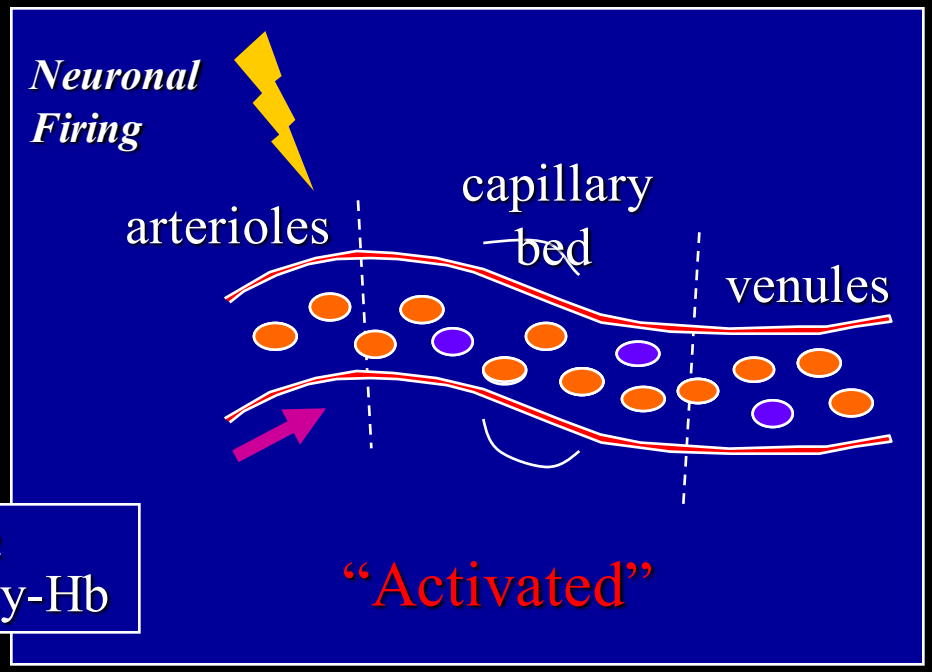


P. A. Bandettini, "Twenty years of functional MRI: the science and the stories," *Neuroimage,* vol. 62, pp. 575-588, Aug 15 2012.

M. J. Lowe, K. E. Sakaie, E. B. Beall, V. D. Calhoun, D. A. Bridwell, M. Rubinov, and S. M. Rao, "Modern Methods for Interrogating the Human Connectome," J Int Neuropsychol Soc, vol. 22, pp. 105-119, Feb 2016.

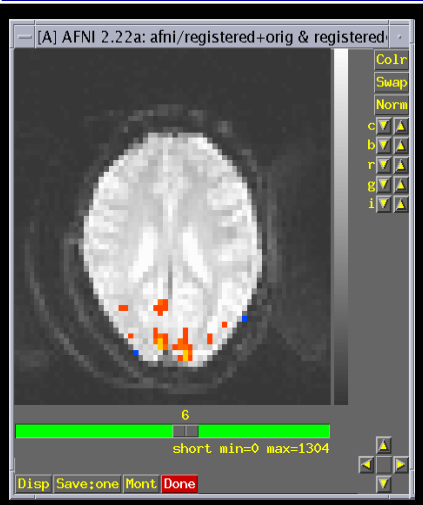
Blood Oxygen Level Dependent (BOLD)

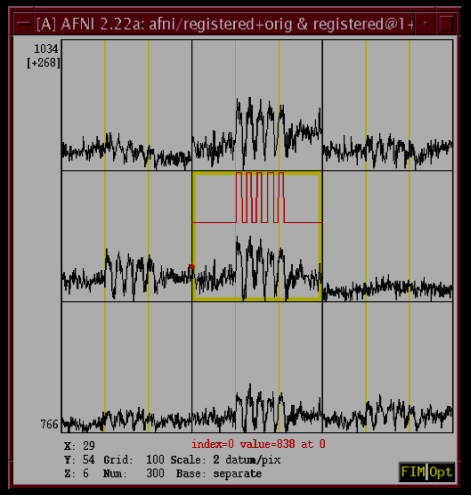




HbO_2
Deoxy-Hb

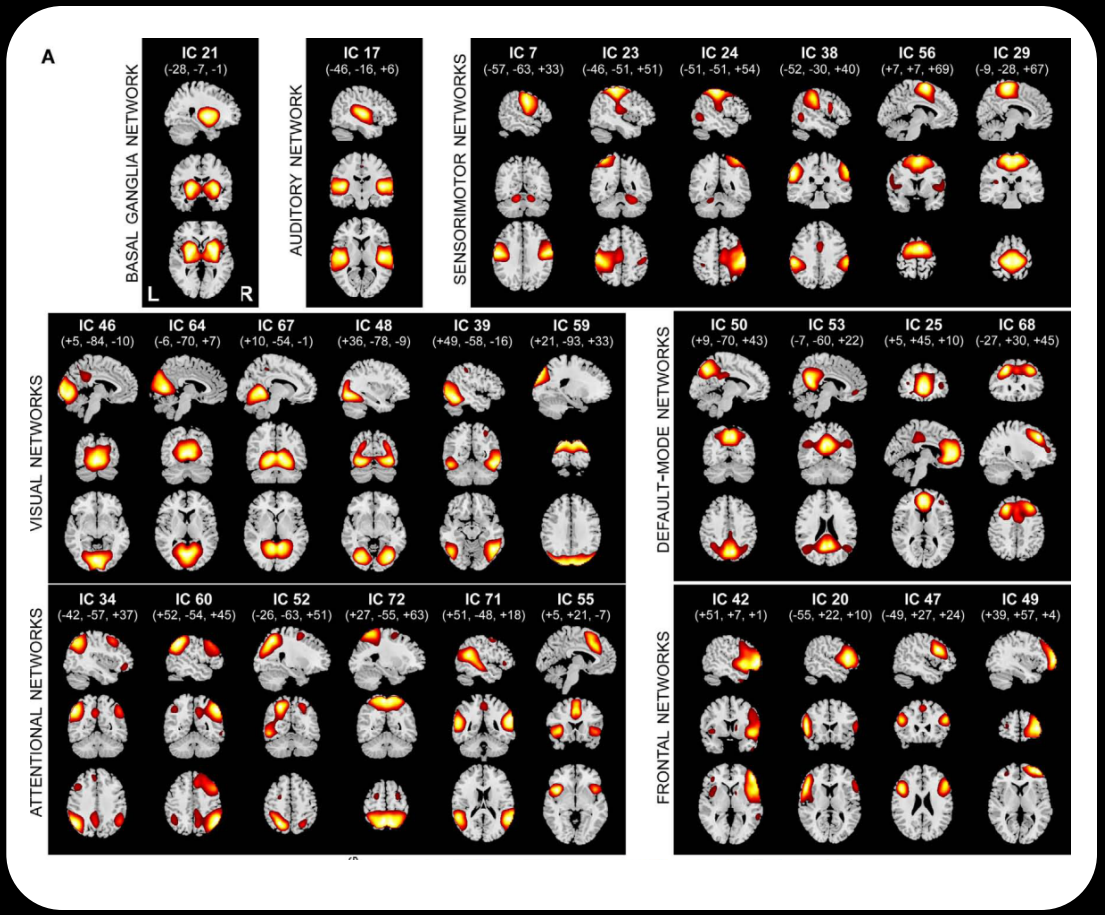
- Neural activity increases
- Blood flow increases ("reactive hyperemia")
- Deoxyhemoglobin concentration decreases
- Magnetic field homogeneity increases
- Gradient echo EPI signal increases



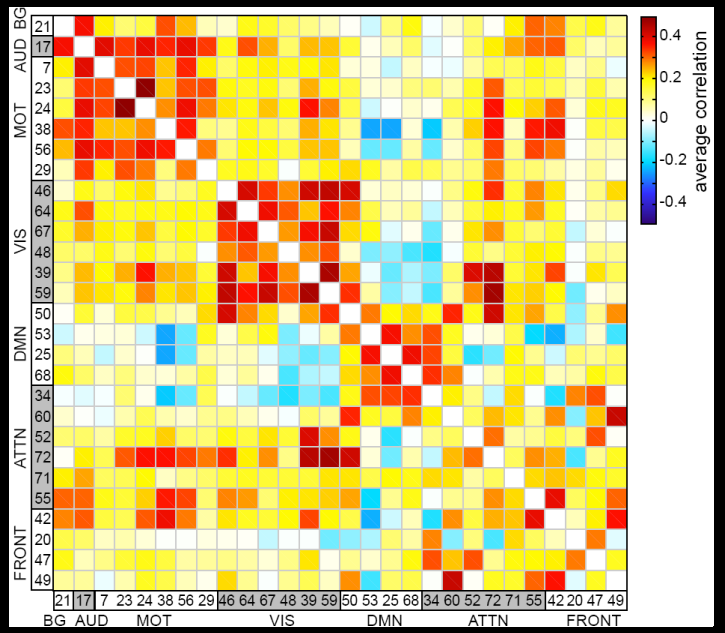


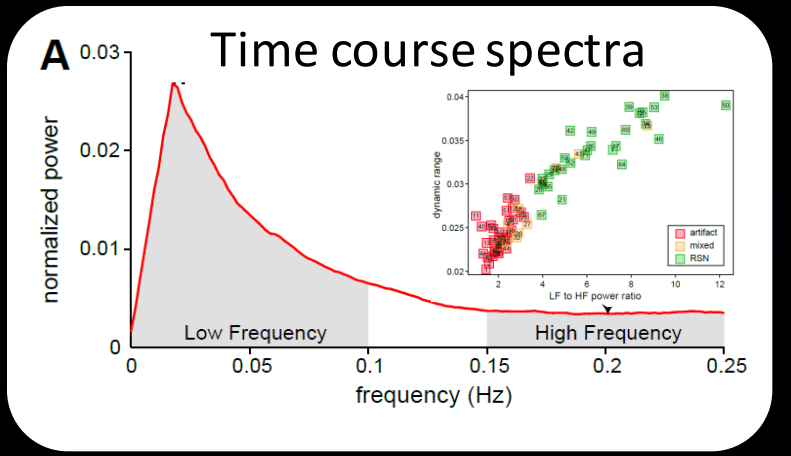
Functional connectivity

Component spatial maps



Functional network connectivity (FNC)





[28 labeled components
& superset of 75 components
N=603 subjects
http://mialab.mrn.org/data]

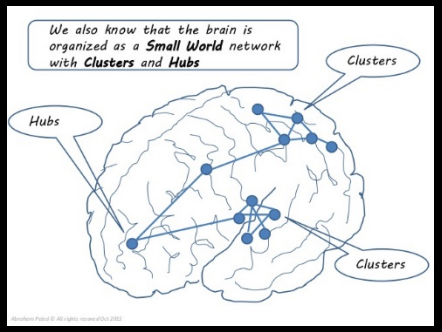
E. Allen, et al, "A baseline for the multivariate comparison of resting state networks," *Frontiers in Systems Neuroscience,* vol. 5, p. 12, 2011.

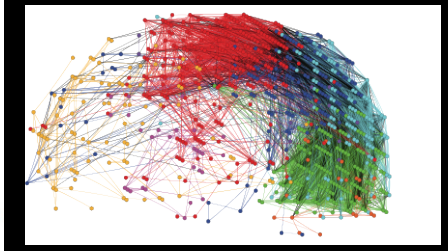
Four key ongoing large-scale efforts

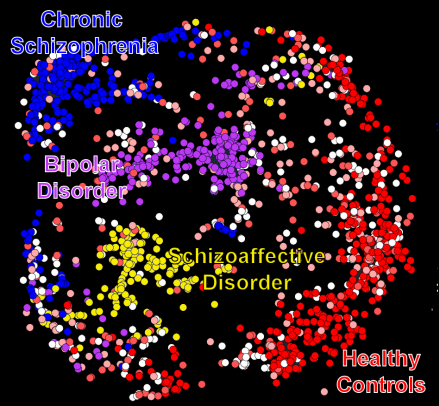
- Big-data to knowledge (BD2K): at least three of the big data centers created are focused on brain imaging (https://datascience.nih.gov/bd2k/funded-programs/centers)
- The Brain Initiative: The focus is on creating new technologies for studying the brain and revealing information we previously did not have access to [http://www.braininitiative.nih.gov/]
- The human connectome project: A large scale effort to standardize data collection and focus on macro-level connectivity (functional and structural)
  http://www.humanconnectomeproject.org/ [MGH/USC]
  http://www.humanconnectome.org/ [WashU]
- The human brain project [EU]. A large scale effort to simulate the human brain (https://www.humanbrainproject.eu/)

Big data approaches

- Available data
  - MRN has a large repository (cf http://coins.mrn.org) including schizophrenia, substance users, etc.
  - The Human Connectome Project has released over 900 subjects (normative) with many more coming
  - The FC1000/INDI project has released over 4,000 data set, a subset with deep phenotyping
- Approaches
  - GLM
  - Graph Theory
  - Matrix Decomposition (PCA, ICA)
  - Deep Learning

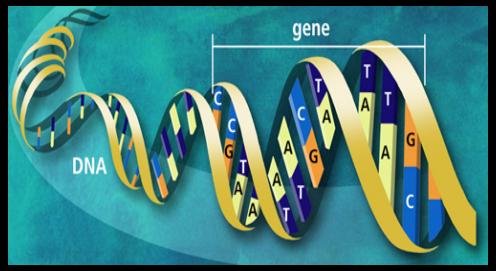


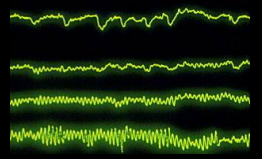


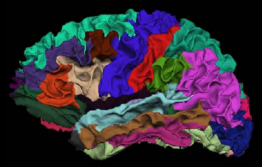


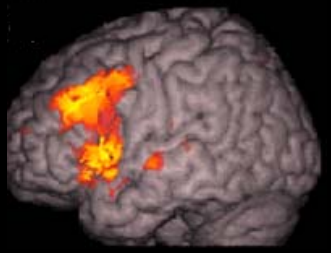
S. Eickhoff, T. E. Nichols, J. D. Van Horn, and J. A. Turner, "Sharing the wealth: Neuroimaging data repositories," *Neuroimage*, vol. 124, pp. 1065-1068, Jan 1 2016.

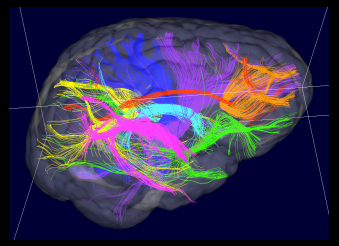
Multimodal Imaging & Genetics

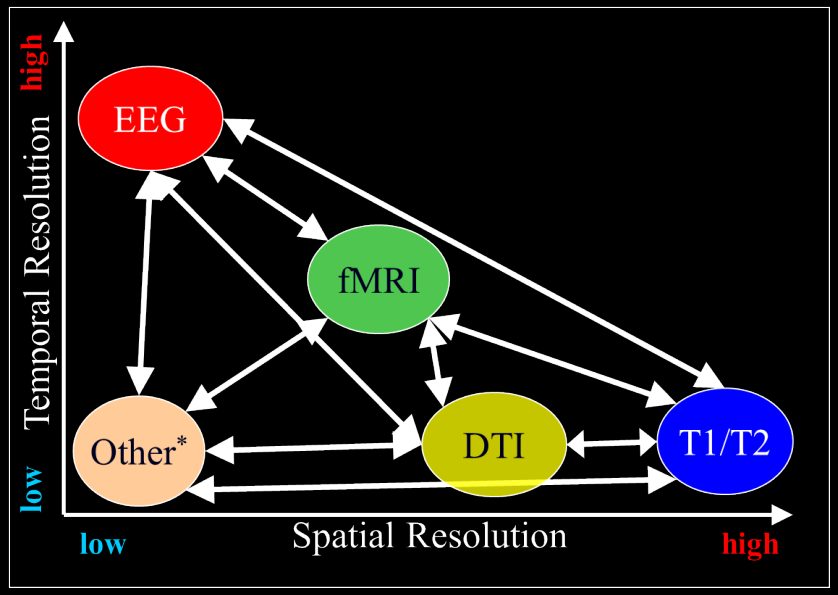


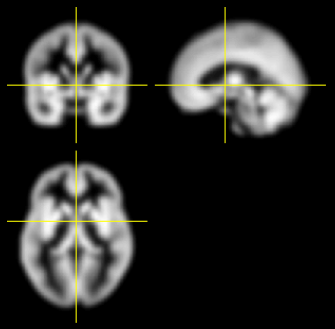


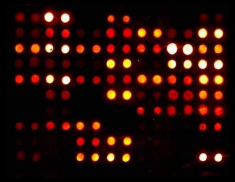












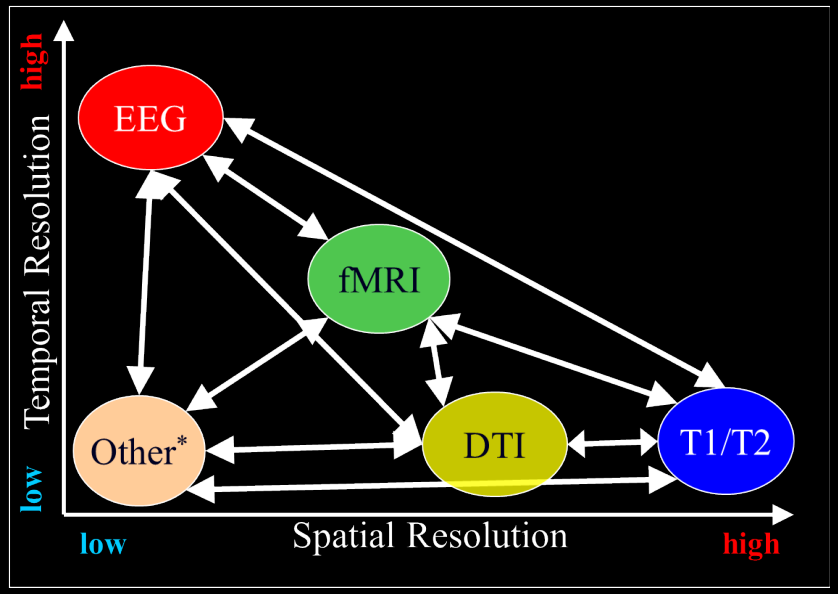
Integration of multimodal data

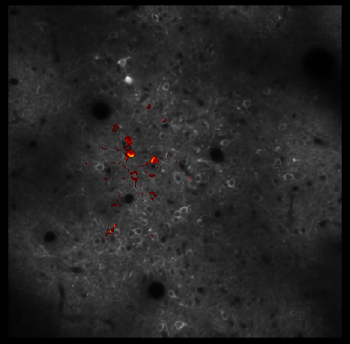
- sMRI
  - Structural images around 1mm^3 are segmented to produce maps of GM/WM
- dMRI
  - Diffusion weighting provide estimates of diffusion at each voxel (e.g. elipses in the case of a tensor)
- fMRI
  - 4D data set of blood-flow collected every 500ms-2s.
- MEG/EEG
  - 64-300 external sensors pick up signals from neurons (either electrical or magnetic) with ms accuracy, but require inverse modeling to infer the location.

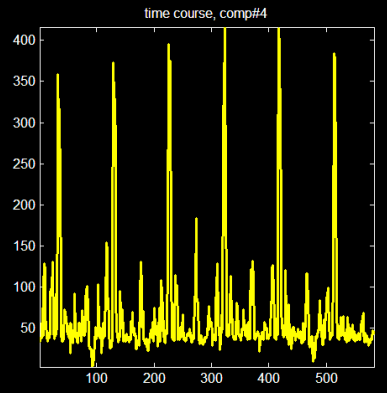
V. D. Calhoun and J. Sui, "Multimodal fusion of brain imaging data: A key to finding the missing link(s) in complex mental illness," *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging,* in press

Bridging spatial/temporal scales

- Examples
  - EEG (ms time, >cm space) -> fMRI (s time, mm space)
  - Bridging human/non-human (animal, dish) through modeling







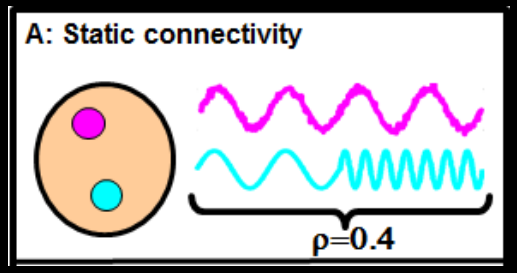
Individualized predictions

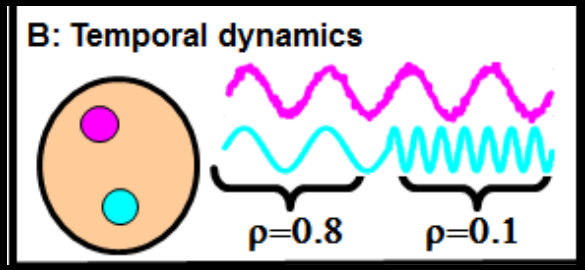
- Predictions of interest include
  - Disease vs health
  - Treatment response (e.g. smoking treatment)
  - Identification of subjects who are more likely to be responsive to a given drug
  - Cognitive scores

M. Arbabshirani, S. Plis, J. Sui, and V. D. Calhoun, "Single Subject Prediction of Brain Disorders in Neuroimaging: Promises and Pitfalls," *NeuroImage,* in press.

Brain dynamics

- The data are 4D, most of the time folks have used models to estimate coupling that is averaged across a given experiment rather than dynamically modeling changes in network structure, etc.





R. M. Hutchison, T. Womelsdorf, E. A. Allen, P. Bandettini, V. D. Calhoun, M. Corbetta, S. D. Penna, J. Duyn, G. Glover, J. Gonzalez-Castillo, D. A. Handwerker, S. D. Keilholz, V. Kiviniemi, D. A. Leopold, F. de Pasquale, O. Sporns, M. Walter, and C. Chang, "Dynamic functional connectivity: promises, issues, and interpretations," NeuroImage, vol. 80, pp. 360-378, 2013, PMC3807588.

V. D. Calhoun, R. Miller, G. Pearlson, and T. Adali, "The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery," *Neuron,* vol. 84, pp. 262-274, Oct 22 2014, PMC4372723.

Informatics solutions

- Lots of repositories, but mostly limited to downloading data and analyzing all at the download site
- Scaling approaches could include decentralized processing (i.e. keep the data local) or computationally efficient approaches for working with large data sets
- Approaches to deal with privacy concerns, reidentification through pattern matching, etc.

S. Eickhoff, T. E. Nichols, J. D. Van Horn, and J. A. Turner, "Sharing the wealth: Neuroimaging data repositories," *Neuroimage,* vol. 124, pp. 1065-1068, Jan 1 2016.

Resources

- MRN (Calhoun, Kiehl)
  - MEG, EEG, MRI
  - Available (preprocessed) data sets
- PCNC (Clark)
  - EEG/tDCS
- CARC (Atlas)
  - Computational resources
- CASAA
  - Substance use expertise
- Others?

Next steps

- Pair-up a brain imaging person with someone who has a relevant approach from a different area
- Identify a funding opportunity (NIH, NSF, DoD, etc)
- Develop a project plan
- Apply for pilot funds
- Acquire or download data, work up some cool results, write up the results and begin to develop the funding application
- Submit the application (repeat from 1 to 10 times)