CONNECTIVITY IN PRACTICE: Syllabus

Michael Peter Milham, MD, PhD

Potental Applications

Recent years have witnessed a rapid transformation in the imaging community, marked by a shift in emphasis from the characterization of regional properties (e.g., task-related activations) to that of functional interactions among regions – termed functional connectivity. In particular, resting state based functional connectivity (RSFC) approaches have taken a lead role in the imaging community, due to their ability to map functional circuits in the brain with great detail and accuracy, and their impressive test-retest reliability and reproducibility across labs. Most excitingly, the relative simplicity of data acquisition and demonstrated ability to pool data across laboratories, have positioned RSFC approaches as a vehicle for discovery science for human brain function.

A diverse array of potential applications exists for functional connectivity approaches, making them relevant to the broader basic, clinical and translational neuroscientific communities. Whether it is the study of human brain function and organization, or the impact of developmental, aging and/or pathologic processes on the brain, RSFC approaches are rapidly providing new insights. The ability to avoid practice, floor and ceiling effects make RSFC ideally suited for application in longitudinal designs, whether observational or treatment-response. Additionally, initial endeavors demonstrating the ability to carry out in vivo comparative functional anatomy studies across species (e.g., humans, primates, rodents) have suggested transformative potential for the application RSFC approaches in translational science.

Examples of each of these applications will be discussed in today's presentation.

Challenges and Considerations

Despite the excitement of RSFC approaches, many considerations need to be taken into account to avoid misinterpretation of results, as well as the potential for artifactual findings. In particular, the need to consider potential cardiovascular physiological signals that can contribute to BOLD signal and possibly confound relationships among regions. Corrections capable of removing such signals have emerged, though require the collection of physiological measures that are not always easy to obtain. Data-driven approaches for physiological correction are also emerging, though their utility requires further validation. To date, the predominant approach is to not correct for these signals – while not damning due to their relatively small contribution to the BOLD signal (< 5-15%), this approach is suboptimal and likely to become more problematic as sample sizes increase.

Beyond respiratory and cardiac signals, another major source of potential confound is the global signal (i.e., mean timeseries for the brain). Once believed to be purely artifactual, the global signal is increasingly believed to contain a component that is a meaningful neurophysiological signal that "yolks" the brain together. Investigators must decide whether to remove this signal or not, in the hopes of revealing more intricate relationships among brain regions that may otherwise be overlooked. In this regard, significant controversy has emerged regarding the best way to remove the global signal. Global signal regression, the predominant approach, has come under increasing scrutiny due to the potential to accentual negative relationships artifactually. Alternative corrections are emerging, though require significant characterization and comparison.

One other noteworthy source of potential artifact in RSFC analyses is head motion. While the functional MRI community is no stranger to the dangers of motion, researchers are increasingly aware of the potential artifactual contributions of motion to the detection of differences among subjects – even at "micro" levels. Similar to global correction and respiratory signal correction, there are approaches for correction emerging, but the field remains without a clear choice.

I bring these various imaging-related source of artifacts to light, not to discourage the usage of RSFC approaches, but rather to increase the attention of users so that analyses are conducted with full

awareness of potential confounds and interrogated thoughtfully. Fortunately, many of these confounds contribute relative small portions of the variance. Though with that said, their effects can potentially sum, and at a minimum will become more prominent as sample sizes increase.

Equally important, though commonly overlooked in the imaging literature are subject-related confounds. Marked variation exists with respect to recruitment strategies, selection criteria and phenotypic characterizations employed across labs. Yet, imaging studies rarely draw attention to this reality. The Attention Deficit Hyperactivity Disorder (ADHD) literature provides an example of an even greater concern – namely, the lack of consideration of clinical heterogeneity. Despite the existence of 3 clinical subtypes (combined type, predominantly inattentive type, predominantly hyperactive type), most ADHD studies treat the disorder as a unitary phenomenon combining behavioral discrete subpopulations into one for the sake of sample size concerns. Such practices may be justifiable if a common neural substrate exists across all subtypes, but there is no clear justification for this to date. ADHD is not unique in the challenge of having to manage clinical heterogeneity in imaging studies. Fortunately, as large samples come into existence (e.g., the ADHD-200 Consortium Sample; http://fcon_1000.projects.nitrc.org/indi/retro/adhd200), so will the potential to turn this weakness into a strength by examining and contrasting the substrates of clinical subtypes and determining the extent to which phenotypic variability is associated with neural variability.

A final consideration as the field moves forward with efforts to use RSFC approaches for neuroscientific and clinical discovery, is the need for large-scale samples. While most datasets remain with less than one hundred participants, early estimates suggest that it will take hundreds of samples to achieve stable results. Until we reach those numbers, we will find marked variation in findings from study to study, as we look from one low-powered sample to the next. Data aggregation efforts (e.g., The 1000 Functional Connectomes Project [FCP] and the International Neuroimaging Data sharing Initiative [INDI]) provide a potential solution to overcoming this challenge, though the obvious cautions are needed when combining uncoordinated datasets across sites.

Recent work highlighting the need for considering these various cautions when attempting to discern brain-behavior relationships will be discussed.

Suggested Readings

Beckmann, C.F.*, et al.* (2005) Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci* 360, 1001-1013

Bilder, R.M.*, et al.* (2009) Phenomics: the systematic study of phenotypes on a genome-wide scale. *Neuroscience* 164, 30-42

Biswal, B.B.*, et al.* (2010) Toward discovery science of human brain function. *Proc Natl Acad Sci U S A* 107, 4734-4739

Buckner, R.L.*, et al.* (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol* 106, 2322-2345

Chang, C.*, et al.* (2009) Influence of heart rate on the BOLD signal: the cardiac response function. *Neuroimage* 44, 857-869

Craddock, R.C.*, et al.* (2009) Disease state prediction from resting state functional connectivity. *Magn Reson Med* 62, 1619-1628

Di Martino, A.*, et al.* (2009) Relationship between cingulo-insular functional connectivity and autistic traits in neurotypical adults. *Am J Psychiatry* 166, 891-899

Dosenbach, N.U.*, et al.* (2010) Prediction of individual brain maturity using fMRI. *Science* 329, 1358-1361

Fox, M.D.*, et al.* (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102, 9673-9678

Fornito, A. and Bullmore, E.T. (2010) What can spontaneous fluctuations of the blood oxygenation-level-dependent signal tell us about psychiatric disorders? *Curr Opin Psychiatry* 23, 239-249

Fransson, P.*, et al.* (2011) The functional architecture of the infant brain as revealed by resting-state fMRI. *Cereb Cortex* 21, 145-154

He, H. and Liu, T.T. (2011) A geometric view of global signal confounds in resting-state functional MRI. *Neuroimage*

Leopold, D.A. and Maier, A. (2011) Ongoing physiological processes in the cerebral cortex. *Neuroimage*

Margulies, D.S.*, et al.* (2010) Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity. *MAGMA* 23, 289-307

Murphy, K.*, et al.* (2009) The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage* 44, 893-905

Raichle, M.E. (2010) Two views of brain function. *Trends Cogn Sci* 14, 180-190

Smith, S.M.*, et al.* (2011) Network modelling methods for FMRI. *Neuroimage* 54, 875-891

Van Dijk, K.R.*, et al.* (2010) Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *J Neurophysiol* 103, 297-321

Van Dijk, K.R.*, et al.* (2011) The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*

Yeo, B.T.*, et al.* (2011) The Organization of the Human Cerebral Cortex Estimated By Functional Connectivity. *J Neurophysiol*

Zuo, X.N.*, et al.* (2010) The oscillating brain: complex and reliable. *Neuroimage* 49, 1432-1445