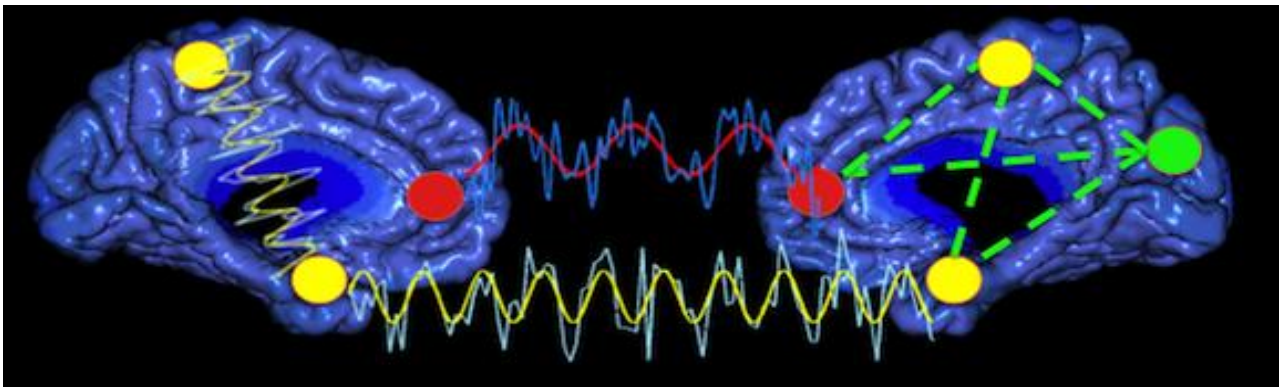

MONTREAL RESTING-STATE fMRI WORKSHOP

May 29, 2014
8:30 – 17:00

Jeanne Timmins Amphitheater
Montreal Neurological Institute

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neuro

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8:45-9:00 Welcome and Introduction

9:00-10:15 RS-fMRI Methods
WHAT MEASURES AND WHICH INFERENCES?

Najmeh Khalili-Mahani, McGill University & Leiden University

Dual Regression versus Eigenvector Centrality Mapping in RSfMRI, a Pharmacological perspective

Since Biswal's report of correlated spontaneous BOLD-signal fluctuations in the motor cortex, numerous evidence have shown that resting-state fMRI is a reliable method for studying the functional topography of brain networks. The rich temporal content of RSfMRI data makes possible to assess several metrics that are potentially informative about the structural and neurophysiological substrates of brain function in health and disease. Independent component and cluster-analysis are extensively used to detect functional networks across distal brain regions sharing similar temporal characteristics. Graph theoretical approaches aim at reducing the data into metrics that reflect the extent and strength of brain network connectivity. There are also various region-of interest analysis techniques that investigate spectral and temporal fluctuations, based on a priori hypothesis about neurophysiological changes. An example from a crossover placebo controlled pharmacological study of alcohol and morphine will be provided to illustrate how three methods (ICA-based dual regression and Eigenvector Centrality Mapping and arterial spin labeling (PCASL)) provide different (and complementary) information about the resting-state functional connectome.

Pierre Bellec, Univérsite de Montréal

Multiscale statistical testing for connectome-wide association studies in fMRI

A recent trend in fMRI connectivity is to systematically test for associations between every possible brain connections (called a connectome) and a disease, instead of focusing on a limited set of a priori regions of interest. Such connectome-wide association studies (CWAS) raise an enormous multiple comparison problem: even with a limited amount of 10^3 of brain parcels, there are in the order of 10^6 univariate tests to perform between every pairs of parcels. A high number of multiple comparisons negatively impacts the sensitivity of the CWAS and also, in practice, limits the ability of the investigator to review all of the results. The number of brain parcels for a CWAS thus appears to have critical implications both in terms of statistical power and interpretability of a CWAS. I will present a new framework called "multiscale statistical parametric connectomes" aimed at identifying a set of data-dependent brain parcels that translates into a good sensitivity for a given CWAS, and also provides a guide to explore the CWAS results with varying degrees of details.

Mona Maneshi, Jean Gotman, Christophe Grova, McGill University

Shared and Specific ICA (SSICA), new data-driven functional connectivity analysis method and its application in epilepsy.

Resting-state fMRI measures the intrinsic function of the brain and investigates how its different parts interact with each other. This technique does not require any experimental design and task performance and therefore is attractive particularly in clinical applications. Independent component analysis (ICA), a popular method to analyze resting-state fMRI data, provides a network view of the changes in brain activity by decomposing the data into independent spatial components. The main limitation of ICA is that it does not simply generalize to draw conclusions about groups of subjects. We recently proposed a new ICA-based method for multi-group comparisons. The method called "shared and specific independent component analysis" or "SSICA" systematically extracts and classifies components (networks) into two categories: those that are common to both groups, and those that are specific to one of the groups. Here, we will first explain the SSICA method and the tests we have performed to examine its validity on synthetic and real neuroimaging data and then will review our recent study, where differences in resting-state networks were investigated between patients with mesial temporal lobe epilepsy (MTLE) and healthy controls.

Coffee Break

10:30-12:00 Neurophysiological Considerations

THE NEUROPHYSIOLOGICAL BASIS OF RESTING BOLD FLUCTUATIONS? (Part 1)

Jean Gotman, McGill University

Interactions between epileptic discharges and the default mode network

BOLD changes related to epileptic discharges can be assessed by combining EEG and fMRI recordings and by comparing the BOLD signal immediately following discharges and discharge-free periods. In this context, most BOLD responses are positive, reflecting the expected intense neuronal activity occurring during the epileptic discharges. Negative BOLD responses have been observed however and they have been more difficult to explain. One of the most commonly observed negative response occurs in the Default Mode Network (DMN). This has been observed principally during generalized spike-wave discharges, but also during some focal epileptic discharges occurring in different brain regions. These often result in negative responses in a subset of the DMN. The mechanisms by which epileptic discharges affect the Default Mode Network remain unknown but it is hypothesized that its deactivation may result in a decreased level of attention during epileptic discharges. Intracerebral EEG studies have demonstrated that deactivation of the DMN during cognitive tasks is accompanied by a decrease in gamma-band activity. We have similarly demonstrated that interictal spikes located far from DMN nodes can result in decreased gamma activity in DMN regions, thus providing a neurophysiological correlate to BOLD findings.

Amir Shmuel, McGill University

Laminar-dependent neurophysiological activity underlying spontaneous fluctuations in hemodynamic signals

Resting-state functional connectivity has been studied using fMRI with regions of interest and network nodes at the functional-spatial scale of cortical areas. Here we tested the hypothesis that resting-state functional connectivity is a phenomenon that can be extended to the scale of cortical layers. We used linear electrode arrays with 32 contacts equally spaced at 100 micron intervals for recordings in the somatosensory cortices of rats. Blood oxygenation signals were measured using optical imaging (OI) simultaneously with neurophysiology. The spatiotemporal structure of spontaneous current source density (CSD) across cortical layers was not homogeneous. Two main laminar clusters were observed based on the positive (CSD in-phase) and negative (CSD out of phase) correlations of spontaneous CSDs within and between clusters, respectively. Cluster analysis showed that the inter-laminar correlation structure of spontaneous-CSD was similar to that of the evoked CSD response, forming consistent clusters. During spontaneous activity, the OI BOLD signals were correlated with neurophysiological gamma Band-Limited-Power (BLP) in layers 2/3-4. We conclude that spontaneous current sources and sinks are neither random nor homogeneous across a cortical column. The influence of neurophysiological activity on BOLD signals is laminar- and frequency band specific. Resting-state functional connectivity, commonly studied at the spatial scale of cortical areas, is a multi-scale phenomenon.

12:00-13:00

Lunch (provided)

13:15-14:15 Multimodal RSfMRI

THE NEUROPHYSIOLOGICAL BASIS OF RESTING BOLD FLUCTUATIONS (Part 2)

Peter Donhauser & Sylvain Baillet, McGill University

Dynamics of cross-frequency coupling in the resting & active states

During the past decade, resting-state networks have been identified with fMRI and more recently, using MEG imaging. Yet, the neurophysiological mechanism explaining the production of these organized fluctuations remains to be uncovered. Here we show non-invasively with MEG source imaging that the nested dynamics of neural oscillations provide a support for long-range, default connectivity in the resting brain. In particular, we confirm that the occurrence of local high-frequency neural oscillations is coupled with the phase of slower fluctuations and demonstrate that it is a ubiquitous phenomenon across the human brain. We further show that this nesting mechanism of phase-amplitude coupling between neural oscillations accounts for the correlated variations of imaging signals from different brain regions that have been observed using other techniques in the resting brain so far. Overall, our results suggest that the mechanisms that reveal the brain's resting-state networks with fMRI are based on the cross-frequency coupling between the phase of low-frequency components and the amplitude of high-gamma oscillatory fluctuations. We will discuss further this generic principle with experimental data illustrating how ongoing resting-state brain dynamics are perturbed by sensory stimulation. We will discuss further this generic principle with experimental and computational modelling results illustrating how ongoing resting-state brain dynamics are perturbed by sensory stimulation.

Oury Monchi, Université de Montréal

Combining TBS and RS-fMRI for the study of fronto-striatal connectivity

The dorsolateral prefrontal cortex (DLPFC) is known to have anatomical connections to multiple brain regions. Here, we explored whether preferential functional interaction exists between the DLPFC, the caudate nucleus, and thalamus, part of the 'cognitive' corticostriatal loop. Young healthy adults underwent three resting-state fMRI sessions, one at baseline, and two following either intermittent (excitatory) or sham theta-burst stimulation (TBS) of the left DLPFC. Average BOLD responses for intermittent TBS compared with the baseline condition revealed significantly increased activity in the left caudate nucleus, thalamus, posterior parietal cortex, and ventrolateral prefrontal cortex. Comparing the intermittent and sham TBS conditions showed significant activation in the left thalamus and a trend in the caudate nucleus. The stimulated site did not reveal significant activation following intermittent TBS vs. baseline nor did it correlate with many regions when using it as a seed in a functional connectivity analysis, suggesting that the strongest effects of TBS are post-synaptic. In contrast, when the caudate nucleus was selected as a seed, significant correlations were observed with the medial prefrontal cortex, and the cingulate gyrus and other cortical and subcortical regions of the 'cognitive' cortico-striatal loop. These results indicate a preferential functional effect of the DLPFC on the caudate nucleus and thalamus when the confound of task-specific co-recruitment was eliminated. This has potential applications for therapies aiming to improve cognitive deficits in Parkinson's disease.

Coffee Break

14:30-16:00 New Frontiers

WHY IS RESTING STATE fMRI A PROMISING RESEARCH TOOL?

Shahab Vahdat & Julien Doyon, Université de Montréal

Sleep-dependent consolidation of motor sequence learning revealed by fMRI

Up to now, the sleep-dependent consolidation process of motor sequence learning (MSL) has been investigated using various methods including offline gains in behavioral performance, savings, and changes in neural activity during task performance. Yet, this memory process has rarely been studied directly by examining the off-line periods during which the motor memory is being consolidated. Here, we tested whether (i) the memory trace can be detected during resting-state and sleep periods following training and (ii) consolidation is simply due to the reactivation of the initial learning-related trace or results from additional modulation of the memory trace during the off-line period. Our findings suggest that the memory trace acquired during motor sequence learning is not only reactivated, but will eventually evolve to the consolidated memory network during non-REM stage 2 and more so during slow-wave sleep. Furthermore, the consolidated memory trace is selectively activated during the resting-state periods on the next day, even before the retest practice session.

Maxime Parent & Pedro Rosa-Neto, McGill University

Functional connectivity impairments in a transgenic rat model of Alzheimer's Disease

The McGill-R-Thy1 APP is a transgenic rat that expresses brain accumulation of the human amyloid protein, a pathological hallmark of Alzheimer's Disease. Using resting-state fMRI, we have measured in a cohort of these rats a progressive decline in functional connectivity of the Default Mode Network. This decline correlates with spatial memory impairments, and appears to precede structural neurodegeneration.

Francois Chouinard, Alan Evans, Pierre Bellec, McGill University

Heritability of Functional Connectivity

Many aspects of human cognition, behavior and neurological disorders are known to be genetically influenced. Compared to behavioural or diagnostic measures, functional connectivity provides a more objective measure of neurobiological variations with genetic factors. While functional connectivity within the default mode network has previously been shown as heritable, a complete map of the heritability of functional connectivity throughout the connectome is still lacking. In this talk, I will provide a short introduction to the concept of heritability and present the first connectome-wide map of the heritability of functional connectivity, using networks derived from the hierarchical clustering of individual and group level estimates of the stability of functional connections. In addition, factors potentially influencing these results such as the number of nodes used to derive the connectome and age-related changes in heritability will be discussed.

16:00-17:00
Discussion Panel

Considerations

Advances and Pitfalls in the Analysis and Interpretation of **Resting-State** FMRI Data
David M. **Cole**, Stephen M. Smith, Christian F. Beckmann
Front Syst Neurosci. 2010; 4: 8. Prepublished online 2010 February 28. Published online 2010 April 6.
doi: 10.3389/fnsys.2010.00008 PMCID: PMC285453

The **Influence** of the **Amplitude** of **Low-Frequency Fluctuations** on **Resting-State Functional Connectivity**
Xin Di, Eun H. Kim, Chu-Chung Huang, Shih-Jen Tsai, Ching-Po Lin, Bharat B. Biswal
Front Hum Neurosci. 2013; 7: 118. Published online 2013 April 2. doi: 10.3389/fnhum.2013.00118 PMCID: PMC3613753

Global and System-Specific **Resting-State** fMRI **Fluctuations** Are Uncorrelated: Principal Component Analysis Reveals Anti-Correlated Networks
Felix Carbonell, Pierre Bellec, Amir Shmuel
Brain Connect. 2011 December; 1(6): 496–510. doi: 10.1089/brain.2011.0065 PMCID: PMC3604782

The impact of global signal regression on **resting state** correlations: Are anti-correlated networks introduced?
Kevin Murphy, Rasmus M. Birn, Daniel A. Handwerker, Tyler B. Jones, Peter A. Bandettini
Neuroimage. Author manuscript; available in PMC 2009 September 24.
Published in final edited form as: Neuroimage. 2009 February 1; 44(3): 893–905. Published online 2008 October 11. doi: 10.1016/j.neuroimage.2008.09.036 PMCID: PMC2750906

Trouble at Rest: How Correlation Patterns and Group Differences Become Distorted After Global Signal Regression
Ziad S. Saad, Stephen J. Gotts, Kevin Murphy, Gang Chen, Hang Joon Jo, Alex Martin, Robert W. Cox
Brain Connect. 2012 February; 2(1): 25–32. doi: 10.1089/brain.2012.0080 PMCID: PMC3484684

Neurovascular factors in resting-state functional MRI.
Liu TT.
Neuroimage. 2013 Oct 15;80:339-48. doi: 10.1016/j.neuroimage.2013.04.071. Epub 2013 May 1. **Review**. PMID: 23644003

Dynamic functional connectivity: promise, issues, and interpretations.
Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, Della Penna S, Duyn JH, Glover GH, Gonzalez-Castillo J, Handwerker DA, Keilholz S, Kiviniemi V, Leopold DA, de Pasquale F, Sporns O, Walter M, Chang C.

Behavioral interpretations of intrinsic connectivity networks.
Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, Glahn DC, Beckmann CF, Smith SM, Fox PT.
J Cogn Neurosci. 2011 Dec;23(12):4022-37. doi: 10.1162/jocn_a_00077. Epub 2011 Jun 14. PMID: 21671731

Characterizing variation in the functional connectome: promise and pitfalls.
Kelly C, Biswal BB, Craddock RC, Castellanos FX, Milham MP.
Trends Cogn Sci. 2012 Mar;16(3):181-8. doi: 10.1016/j.tics.2012.02.001. Epub 2012 Feb 15. **Review**.
PMID:22341211