Time-varying connectivity in resting-state fMRI: methods, interpretations and clinical use.

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Recent converging evidence suggests that a static representation of FC, e.g. based on the correlation between entire fMRI time series, misses important information encoded in fMRI data. Hence, various methods have been developed in recent years to exploit the information encoded beyond such static measures. The researcher interested in exploring time-varying FC properties has to select among the multitude of proposed methods, each one having different properties and underlying assumptions. The goal of this course is to provide guidance in the choice of an adequate time-varying FC method to address a specific neuroscientific question. In the first part of the course we will recall the definitions of the most important mathematical notions required to characterize temporal fluctuations of functional connectivity. Then, we will provide an overview of the main approaches used to explore functional connectivity beyond the classical static paradigm (e.g. brain states, co-activation patterns, autoregressive models), including concrete examples of how these methods have been used in clinical applications. The second part of the course will be devoted to the interpretation of FC fluctuations. We will detail their links to micro-scale (i.e. neuronal) dynamics as well as their behavioral counterparts. We will conclude by summarizing the main remaining controversies of the field. In order to maximize learning outcomes for participants, we will discuss multiple-choice questions at the end of each talk, and take questions from the audience using the OHBM interactive tool.

We finally note that last year's course room was overfull, with many attendees standing or sitting on the ground and others not being able to enter the room (this was to a lesser extent also the case in OHBM-Singapore). We believe this further reflects the interest of our community in the proposed course.

Objective

1. Definition of various terms important to the study of time-varying connectivity including 'stationary', 'dynamic', 'static', 'time-varying'

2. Step-by-step explanation of popular methods used to explore the time-varying nature of FC (including demos using popular toolboxes) and application to real datasets
3. Interpretation of the temporal fluctuations of FC in terms of (i) links to micro-scale (neuronal) dynamics and (ii) behavioral counterparts.

Target Audience

The target audience for this course are researchers interested in (the time-varying properties of) functional connectivity. While we will mainly discuss FC evaluated from fMRI data with some emphasis on multimodal studies as well. The proposed theoretical background and interpretations can be applied to any modality involving time series (e.g. MEG, EEG).

Presentations

Going beyond the static functional connectome: a theoretical and methodological framework

In this introductory talk, we first review the main theoretical notions necessary to characterize the vast repertoire of methods extending static models of the functional connectome (FC). We make the distinction between "time-varying" approaches that exploit temporal fluctuations of functional interactions, and "dynamic" frameworks that use time series models. The most common time-varying method consists in computing pairwise correlations between fMRI time courses of different brain regions using a sliding-window framework. We introduce its use, and discuss the improvements that have been proposed, concerning in particular: (1) the choice of the most suitable window characteristics; (2) alternative metrics to assess FC inside the window; (3) how to extract interpretable information from the FC patterns, i.e. by determining FC states. Then, the simplest dynamic model of the functional connectome relies on autoregressive models of neuroimaging time series. We will review its use, applications, and compare the properties of dynamic and time-varying approaches. Finally, we introduce some promising alternatives to these classical approaches, including framewise-based analyses and nonlinear time series models.

Presenter

Maria Giulia Preti, École Polytechnique Fédérale de Lausanne Geneva, Geneva
Switzerland

How null-models can (or not) be used to detect time-varying functional connectivity

Null-models are widely used as a means to generate surrogate data and explore data properties. Various null-models have been proposed to refine the characterization of neuroimaging time series, but the interpretation of null-model testing should be cautious. In this talk, I will first introduce the basic theoretical foundations of null-model testing. In particular I will show that in most cases, more than one statistical property is attached to a given null-model. Therefore, the outcome of the corresponding tests might in general have multiple interpretations. I will then present the most popular null-models of neuroimaging data and detail which statistical properties they are testing for. I will conclude by emphasizing that instead of testing for the presence or absence of "time-varying" of "dynamic" functional connectivity, null-models should rather be used to characterize the nature of the temporal fluctuations of neuroimaging metrics.

Presenter

Raphael Liegeois, École Polytechnique Fédérale de Lausanne Geneva, Geneva
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Time-varying connectivity: Data-driven approaches and clinical applications

The study of complex mental illness can greatly benefit from flexible analytic approaches. In particular, the advent of data-driven approaches to identify time-varying connectivity and activity has revealed a number of interesting clinically-relevant variation in the data which, when ignored, can provide misleading information. In this lecture I will provide a comparative introduction of a range of data-driven approaches to estimating time-varying connectivity. I will also present detailed examples where studies of mental illness have been advanced by approaches designed to capture and estimate time-varying information in resting fMRI data. As part of this, I will review several exemplar data sets analyzed in different ways to demonstrate the complementarity as well as trade-offs of various modeling approaches to answer questions about complex mental illness. Finally, I will review and provide examples of strategies for validating TVC including simulations, multimodal imaging, and comparative prediction within clinical populations, among others. As part of the interactive aspect I will provide a hands-on guide to the dynamic functional network connectivity toolbox within the GIFT software, including an online didactic analytic decision tree to introduce the various concepts and decisions that need to be made when using such tools.

Presenter

Vince Calhoun, Georgia State/Georgia Tech/Emory
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Neuronal models of dynamic functional connectivity: Linking scales and data modalities.

Dynamic functional connectivity arises from complex patterns of activity in large-scale neuronal systems. In this talk, I will introduce the basic approach to understanding and modelling neuronal dynamics across different spatial and temporal scales. I will explain how large-scale brain dynamics in circuits and networks can arise from the collective activity amongst individual neurons, and how slow dynamics (on the time-scale of the BOLD signal) emerge from fluctuations in fast spiking neurons. Candidate dynamic mechanisms of dynamic functional connectivity include metastability, criticality and multistability which reflect different types of instabilities in a complex system. I will end with a hands-on guide to the main toolboxes that researchers can use to model these dynamics.

Presenter

Michael Breakspear, University of Newcastle Newcastle, New South Wales
Australia

Wandering around functionally relevant Network States

Functionally-relevant network patterns form transiently in brain activity during rest, where a given subset of brain areas exhibits temporally synchronized BOLD signals. To adequately asses the biophysical mechanisms driving resting-state activity, a detailed characterization of the dynamical features of functional networks is needed from the experimental side to inform theoretical models. Borrowing tools from Dynamical Systems' Theory, such as Markovian chains, dwelling times, recurrence times and switching probabilities, one can characterize resting-state brain dynamics in the form of trajectories within a low-dimensional state space, providing insights into the universal principles governing brain activity in the spontaneous state. In this framework, functional brain subsystems emerge as recurrent ghost-attractors whose properties appear consistent across healthy subjects but appear disrupted in neuropsychiatric disorders, reinforcing the importance of addressing dynamical features of functional brain networks to gain insight into brain function.

Presenter

Joana Cabral, University of Oxford Oxford, Oxford
United Kingdom

Timescales of variation in human functional brain networks

Functional connectivity may be used for a variety of applications, from identification of brain disorder biomarkers to measuring task states and spontaneous cognition. These applications depend on functional networks exhibiting variation at very different timescales. In this presentation, we will review evidence that fMRI functional networks are largely stable, driven by group commonalities and individual features. Variation at faster time-scales (due to day-to-day or task-state differences) is also evident, but substantially smaller in magnitude. Once artifacts are accounted for, we find that variation in functional connectivity during resting-state is primarily driven by differences in arousal. We will close by discussing implications of these findings for applications of functional connectivity.

Presenter

Caterina Gratton, Northwestern Evanston, IL
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