Time-varying Connectivity in Resting-state fMRI: Methods, interpretations, and clinical use

Vince Calhoun Co Organizer
GSU/GATech/Emory
TReNDS Center
Atlanta, GA
United States

Raphael Liegeois Organizer
École Polytechnique Fédérale de Lausanne
Geneve, Vaud
Switzerland

Educational Course - Half Day

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, spatial vs temporal dynamics), 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 and ongoing lines of inquiry in 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 virtual course attendance was high (as for the previous in person meeting in OHBM-Rome for which the room was overflowing). We believe this further reflects the interest of our community in the proposed course.

Objective

- Definition of various terms important to the study of time-varying connectivity including 'stationary', 'dynamic', 'static', 'time-varying'
- 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
- 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 is the computation of 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, and compare the properties of dynamic and time-varying approaches. Lastly, we introduce some promising alternatives to these classical approaches, including framewise-based analyses and nonlinear time series models. We highlight their applications, in particular, in characterizing alterations in brain dynamics across various brain states, such as during sleep and wakefulness.

Presenter

Anjali Tarun, University of Lausanne Lausanne, Vaud, Switzerland

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Interpreting Null Models of Time-varying FMRI

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 Geneve, Vaud, Switzerland

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, GSU/GATech/Emory, TReNDS Center, Atlanta, GA, United States

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Mechanistic Principles of Resting-State Networks and Their Modulation Over Time

Resting-state networks (RSNs) have been consistently detected across fMRI neuroimaging studies and their integrity has been implicated in a wide variety of neurological and psychiatric disorders. However, the principles governing the emergence and modulation of RSNs remain unclear, hindering the advance in therapeutic strategies targeted at rebalancing RSN dynamics. In this workshop, I will describe a novel methodological approach to characterize the dynamical properties of RSNs revealing their intrinsic oscillatory nature. In this mechanistic scenario, whole-brain activity can be decomposed into a discrete number of macroscopic oscillatory modes whose power is modulated over time. Each oscillatory mode is characterized by a pattern of phase-locking (detected using leading eigenvector dynamics analysis, LEiDA), where the brain subsystems yielding RSNs are aligned in phase but phase-lagged with respect to the rest of the brain. This scenario is validated by simulating the brain activity of a range of healthy participants, where each individual is associated to a characteristic modulation of the power of each oscillatory mode over time. We demonstrate that individual differences in resting-state functional connectivity metrics (assessed using graph theory and dynamical analysis) can be retrieved, reinforcing the validity of this mechanistic model to represent resting-state activity across healthy subjects. To engage the audience in a virtual environment, multiple choice questions will be included, and a toolbox with the codes for analysis and simulation demonstrated in the workshop will be shared with attendees.

Presenter

Joana Cabral, University of Minho Minho, Minho, Portugal

Biophysical 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 modelling neuronal dynamics across different spatial and temporal scales. I will explain candidate mechanisms causing dynamic functional connectivity include metastability, criticality and multistability. This will lead to the various means of analysing empirical data, such as the use of the Hidden Markov Model. The influence of neuromodulatory systems on system-wide brain dynamics will also be discussed. I will end with a hands-on guide to the main toolboxes that researchers can use to forward simulate these dynamics and to analyse empirical data using custom toolboxes.

Presenter

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

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Timescales of Variation in Human Functional Brain Networks

In recent years, there has been interest in using fMRI functional connectivity for a variety of applications, from identification of disease 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 from our work suggesting that fMRI functional networks are largely stable, dominated 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 associated with differences in arousal. We introduce metrics for evaluating the stability/non-stationarity of functional connectivity and introduce publicly-available code for contrasting experimental fMRI data with null simulations that match fMRI functional connectivity spectral and network structure. We will close by providing a set of methodological recommendations and points for future research.

Presenter

Caterina Gratton, Northwestern University Evanston, IL, United States