Discovery of key whole-brain transitions and dynamics during human wakefulness and non-REM sleep

The modern understanding of sleep is based on the classification of sleep into stages defined by their electroencephalography (EEG) signatures, but the underlying brain dynamics remain unclear. Here we aimed to move significantly beyond the current state-of-the-art description of sleep, and in particular to characterise the spatiotemporal complexity of whole-brain networks and state transitions during sleep. In order to obtain the most unbiased estimate of how whole-brain network states evolve through the human sleep cycle, we used a Markovian data-driven analysis of continuous neuroimaging data from 57 healthy participants falling asleep during simultaneous functional magnetic resonance imaging (fMRI) and EEG. This Hidden Markov Model (HMM) facilitated discovery of the dynamic choreography between different whole-brain networks across the wake-non-REM sleep cycle. Notably, our results reveal key trajectories to switch within and between EEG-based sleep stages, while highlighting the heterogeneities of stage N1 sleep and wakefulness before and after sleep.

Evaluating Models of Dynamic Functional Connectivity Using Predictive Classification Accuracy

Dynamic functional connectivity has become a prominent approach for tracking the changes of macroscale statistical dependencies between regions in the brain. Effective parametrization of these statistical dependencies, referred to as brain states, is however still an open problem. We investigate different emission models in the hidden Markov model framework, each representing certain assumptions about dynamic changes in the brain. We evaluate each model by how well they can discriminate between schizophrenic patients and healthy controls based on a group independent component...
analysis of resting-state functional magnetic resonance imaging data. We find that simple emission models without full covariance matrices can achieve similar classification results as the models with more parameters. This raises questions about the predictability of dynamic functional connectivity in comparison to simpler dynamic features when used as biomarkers. However, we must stress that there is a distinction between characterization and classification, which has to be investigated further.

Functional Connectivity using a Wishart Mixture Model

Modeling Temporal Dynamics in Functional Brain Connectivity

This thesis deals with modeling temporal changes in functional brain connectivity derived from functional magnetic resonance imaging (fMRI). These changes, observed in both task and rest settings, have been coined dynamic functional connectivity (dFC), and are often clustered into a discrete set of so-called dFC states. In the five included research papers, we analyse these repeating patterns of connectivity using Bayesian machine learning methods and relate these to cognitive traits and disease status in different resting-state datasets. In dFC state models, we are faced with many parameter choices, which we in this thesis have tackled using a predictive likelihood framework allowing for quantitative model comparison. Furthermore, this can also be used to assess the relative plausibility of a set of candidate models. We applied this framework to the Wishart mixture model, a probabilistic extension of the sliding-window k-means approach used in many dFC studies. Here, we show that the predictive likelihood can be used to quantify the support for dFC given different window lengths. Furthermore, in another paper we show that the predictive likelihood can be used to choose both the number of states and the model structure in a hidden Markov model (HMM) applied to a highly sampled single subject's resting-state fMRI data. Another way to investigate the relevance of dFC models is to relate them to subject specific cognitive traits or disease status. The former was investigated in a large cohort of healthy subjects' resting-state fMRI data and we found almost no association between the temporal characteristics of the dFC models and the higher order cognitive traits. In another paper we investigated different HMMs ability to distinguish between patients with schizophrenia and healthy controls based on resting-state fMRI data. We found that the simplest characterizations using static FC were adequate for the classification task. Our findings underline the importance of quantitative evaluation of dFC models and furthermore shows that we need better models that can account for subject variability and noise confounds.
Predictive assessment of models for dynamic functional connectivity

In neuroimaging, it has become evident that models of dynamic functional connectivity (dFC), which characterize how intrinsic brain organization changes over time, can provide a more detailed representation of brain function than traditional static analyses. Many dFC models in the literature represent functional brain networks as a meta-stable process with a discrete number of states; however, there is a lack of consensus on how to perform model selection and learn the number of states, as well as a lack of understanding of how different modeling assumptions influence the estimated state dynamics. To address these issues, we consider a predictive likelihood approach to model assessment, where models are evaluated based on their predictive performance on held-out test data. Examining several prominent models of dFC (in their probabilistic formulations) we demonstrate our framework on synthetic data, and apply it on two real-world examples: a face recognition EEG experiment and resting-state fMRI. Our results evidence that both EEG and fMRI are better characterized using dynamic modeling approaches than by their static counterparts, but we also demonstrate that one must be cautious when interpreting dFC because parameter settings and modeling assumptions, such as window lengths and emission models, can have a large impact on the estimated states and consequently on the interpretation of the brain dynamics.

Testing group differences in state transition structure of dynamic functional connectivity models

Understanding the origins of intrinsic time-varying functional connectivity remains a challenge in the neuroimaging community. However, some associations between dynamic functional connectivity (dFC) and behavioral traits have been observed along with gender differences. We propose a permutation testing framework to investigate dynamic differences between groups of subjects. In particular, we investigate differences in fractional occupancy, state persistency and the full transition probability matrix. We demonstrate our framework on resting state functional magnetic resonance imaging data from 820 healthy young adults from the Human Connectome Project considering two prominent dFC models, namely sliding-window k-means and the Gaussian hidden Markov model. The variables showing consistent significant dynamic differences were limited to gender and the degree of motion in the scanner. We observe for the data considered that a large sample size (here 500 subjects) is needed to to draw reliable conclusions about the significance of those variables. Our results point to dynamic features providing limited information with regard to behavioral traits despite a relatively large sample size.
Variational bayesian partially observed non-negative tensor factorization

Non-negative matrix and tensor factorization (NMF/NTF) have become important tools for extracting part based representations in data. It is however unclear when an NMF or NTF approach is most suited for data and how reliably the models predict when trained on partially observed data. We presently extend a recently proposed variational Bayesian NMF (VB-NMF) to non-negative tensor factorization (VB-NTF) for partially observed data. This admits bi- and multi-linear structure quantification considering both model prediction and evidence. We evaluate the developed VB-NTF on synthetic and a real dataset of gene expression in the human brain and contrast the performance to VB-NMF and conventional NMF/NTF. We find that the gene expressions are better accounted for by VB-NMF than VB-NTF and that VB-NMF/VB-NTF more robustly handle partially observed data than conventional NMF/NTF. In particular, probabilistic modeling is beneficial when large amounts of data is missing and/or the model order over-specified.

Modeling dynamic functional connectivity using a wishart mixture model

Dynamic functional connectivity (dFC) has recently become a popular way of tracking the temporal evolution of the brains functional integration. However, there does not seem to be a consensus on how to choose the complexity, i.e. number of brain states, and the time-scale of the dynamics, i.e. the window length. In this work we use the Wishart Mixture Model (WMM) as a probabilistic model for dFC based on variational inference. The framework admits arbitrary window lengths and number of dynamic components and includes the static one-component model as a special case. We exploit that the WMM framework provides model selection by quantifying models generalization to new data. We use this to quantify the number of states within a prespecified window length. We further propose a heuristic procedure for choosing the window length based on contrasting for each window length the predictive performance of dFC models to their static counterparts and choosing the window length having largest difference as most favorable for characterizing dFC. On synthetic data we find that generalizability is influenced by window length and signal-tonoise ratio. Too long windows cause dynamic states to be mixed together whereas short windows are more unstable and influenced by noise and we find that our heuristic correctly identifies an adequate level of complexity. On single subject resting state fMRI data we find that dynamic models generally outperform static models and using the proposed heuristic points to a windowlength of around 30 seconds provides largest difference between the predictive likelihood of static and dynamic FC.
Scalable group level probabilistic sparse factor analysis

Many data-driven approaches exist to extract neural representations of functional magnetic resonance imaging (fMRI) data, but most of them lack a proper probabilistic formulation. We propose a scalable group level probabilistic sparse factor analysis (psFA) allowing spatially sparse maps, component pruning using automatic relevance determination (ARD) and subject specific heteroscedastic spatial noise modeling. For task-based and resting state fMRI, we show that the sparsity constraint gives rise to components similar to those obtained by group independent component analysis. The noise modeling shows that noise is reduced in areas typically associated with activation by the experimental design. The psFA model identifies sparse components and the probabilistic setting provides a natural way to handle parameter uncertainties. The variational Bayesian framework easily extends to more complex noise models than the presently considered.

Variational group-PCA for intrinsic dimensionality determination in fMRI data

Functional Magnetic Resonance Imaging (fMRI) is widely used to gain a better understanding of the human brain's functional organization. As fMRI data are high dimensional it is challenging to analyse using conventional methods such as principal component analysis (PCA), and independent component analysis (ICA) is often applied as a preprocessing step before any additional analysis. Low-rank methods generally require that the rank or latent dimensionality is known beforehand. When this is not the case a range of plausible dimensionalities have to be tested and compared. Furthermore, in an fMRI-context it is not fully understood how information from multiple subjects should best be
incorporated when applying dimensionality reduction. We propose a Bayesian group principal component analysis (Group-BPCA) model with an automatic relevance determination (ARD) prior to determine the number of active components supported by the data. All subjects share the same spatial maps (components), but the uncertainties on these maps as well as the noise is subject specific. We find an approximate solution using the mature variational Bayesian framework and develop a fast and scalable implementation using a graphical processing unit (GPU). We test the model on fMRI data from 29 healthy subjects performing a block-design fingertapping experiment. The model identified 10 active components. Neither variational Bayesian PCA on temporally concatenated data nor Group-BPCA, where uncertainties on the spatial maps are shared, leads to pruning components, but provide better generalization in two of three scenarios. We show that the right level of subject variability is highly dependent on the chosen validation scheme.

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**Nonparametric modeling of dynamic functional connectivity in fMRI data**

Dynamic functional connectivity (FC) has in recent years become a topic of interest in the neuroimaging community. Several models and methods exist for both functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), and the results point towards the conclusion that FC exhibits dynamic changes. The existing approaches modeling dynamic connectivity have primarily been based on time-windowing the data and k-means clustering. We propose a nonparametric generative model for dynamic FC in fMRI that does not rely on specifying window lengths and number of dynamic states. Rooted in Bayesian statistical modeling we use the predictive likelihood to investigate if the model can discriminate between a motor task and rest both within and across subjects. We further investigate what drives dynamic states using the model on the entire data collated across subjects and task/rest. We find that the number of states extracted are driven by subject variability and preprocessing differences while the individual states are almost purely defined by either task or rest. This questions how we in general interpret dynamic FC and points to the need for more research on what drives dynamic FC.

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Non-negative Tensor Factorization with missing data for the modeling of gene expressions in the Human Brain

Non-negative Tensor Factorization (NTF) has become a prominent tool for analyzing high dimensional multi-way structured data. In this paper we set out to analyze gene expression across brain regions in multiple subjects based on data from the Allen Human Brain Atlas [1] with more than 40% data missing in our problem. Our analysis is based on the non-negativity constrained Canonical Polyadic (CP) decomposition where we handle the missing data using marginalization considering three prominent alternating least squares procedures; multiplicative updates, column-wise, and row-wise updating of the component matrices. We examine three gene expression prediction scenarios based on data missing at random, whole genes missing and whole areas missing within a subject. We find that the column-wise updating approach also known as HALS performs the most efficient when fitting the model. We further observe that the non-negativity constrained CP model is able to predict gene expressions better than predicting by the subject average when data is missing at random. When whole genes and whole areas are missing it is in general better to predict by subject averages. However, we find that when whole genes are missing from all subjects the model based predictions are useful.

When analyzing the structure of the components derived for one of the best predicting model orders the components identified in general constitute localized regions of the brain. Non-negative tensor factorization based on marginalization thus forms a promising framework for imputing missing values and characterizing gene expression in the human brain. However, care also has to be taken in particular when predicting the genetic expression levels at a whole region of the brain missing as our analysis indicates that this requires a substantial amount of subjects with data for this region in order for the model predictions to be reliable.

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