NEUROIMAGING-GENETICS DATA ANALYSIS WORKSHOP

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ABSTRACTS

❖ Gunter Schuhmann

The IMAGEN study: Gene x neuroimaging analysis of reward and substance use behaviour in 14 year old adolescents.

A fundamental function of the brain is to evaluate the emotional and motivational significance of stimuli and to adapt behaviour accordingly. The IMAGEN study is the first multicentre genetic-neuroimaging study aimed at identifying the genetic and neurobiological basis of individual variability in impulsivity, reinforcer sensitivity and emotional reactivity, and determining their predictive value for the development of frequent psychiatric disorders.
We have conducted comprehensive behavioural and neuropsychological characterization, functional and structural neuroimaging and genome-wide association analyses of 2000 14-year-old adolescents combined with functional genetics in animal and human models.
In this presentation we will present data on neurobiological mechanisms of the disposition to addictive behaviour with particular focus on reward-related behaviour. We will present associations of brain activation during the Monetary Incentive Delay task with neuropsychological measures of reward and measures of addictive behaviour, including age of onset of alcohol drinking. Furthermore, we will present results of our gene x neuroimaging analyses.

❖ Geoffrey Tan

Imaging approaches to understanding and translating genetic associations in neurology

Neurogenetics has traditionally been a field centering on rare mutations with Mendelian inheritance and striking disease phenotypes. The explosion in genome-wide association studies in recent years has culminated in the discovery of a number of common genetic variants associated with risk for neurological disease and I argue that imaging provides the fine scalpel needed to detect their relatively subtle phenotypes. I will describe work by my colleagues and myself from the Wood and Frackowiak groups where imaging is used to understand the neural correlates of disease causing mutations in DYT1 dystonia and pre-clinical Huntington's, as well as of risk variants for autism, Alzheimer's disease and Parkinson's and discuss the clinical implications of these findings and the likely opportunities for translation in the field of imaging genetics. I will highlight the importance of gene by disease interactions using the example of DYT1 and the opportunities presented by gene carriers and pre-clinical imaging phenotypes to develop measures for early disease detection and therapeutic trials. I will then discuss the influence of KIBRA, microsatellite polymorphisms in ESR2 and AR on endophenotypes such as hippocampal volume as it relates to Alzheimer's disease. I also describe differences in personality and deficits in fronto-occipital circuitry apparent in a polymorphism in CNTNAP2 that is implicated in autistic spectrum disorder, before discussing ongoing work characterising genetic associations found in Parkinson's using candidate and SNP chip data. Thus beyond helping to understand pathogenesis, neuroimaging and genetics can potentially inform diagnostic classification in the field of neurology, provide early markers for detection and indicate neural circuits for therapeutic intervention.

❖ Stéphane Robin

Deciphering network structure via stochastic blockmodel

State space models constitute a natural way to describe a latent, unobserved structure that causes heterogeneity in the observed data. The stochastic block model is a mixture model for graphs where the nodes are supposed to belong to unobserved classes, that are to be recovered.
As for most incomplete data model, the statistical inference is not straightforward. Variational inference provides a general framework to achieve approximate maximum likelihood inference in such a situation. We will show that, the variational approximation is efficient in this case of network.
As the stochastic blockmodel performs model-based clustering for network, it also allows to account for covariates. We will illustrate these works with applications in molecular biology and ecology.

❖ Camille Charbonnier

Inference of sparse Gaussian graphical models with latent structure

The use of microarrays to discover differentially expressed genes or to cluster genes into groups displaying similar expression patterns has found many applications. These include the identification of biomarkers that may be important in the diagnosis and prognosis of diseases. The challenge lies in translating both lists of differentially expressed genes or cluster of co-regulated genes into a better understanding of the underlying biological phenomena.
We focus on the use of Gaussian Graphical Models (GGMs) to explore what happens at the regulation level, answering the question: how does expression of gene A directly affect expression of gene B? GGMs describe those regulations in terms of conditional dependencies.
In order to cope with the high-dimensional settings, we combine GGMs with recent regularization methods and make use of the structure inherent to biological data to improve inference performances. Indeed, biological networks and particularly gene regulatory networks are known not only to be sparse, but also organized, so that genes tend to connect following specific topological patterns, defined through metabolic pathways or transcription factor binding sites for instance. If topological information can be recovered from existing biological knowledge, we let the possibility to drive the network reconstruction through this prior structure. Otherwise, inference of this latent topological structure can be used to rene the inference of the network.

Structure also arises when various experimental conditions are available, for instance patients versus controls, or placebo versus treatment. In these settings, separate inference in each of the conditions respects the existence of discrepancies in the regulatory chains. However, it neglects all the information that could be gathered if one could assume that most regulations are shared and divergences are indeed the exceptions that we would like to detect. In that perspective, we propose a structured regularizer to jointly estimate these multiple GGMs in a way which admits divergences between the networks. All methodological tools presented here are included in the latest version of the R package SIMoNe.

❖ Roberto Toro

Overview of Phenotypes for Imaging Genetics

Researchers have used various neuroimaging measurements as quantitative endophenotypes in genetic analyses to look for the biological processes that underlie functional and structural brain variability. Neuroimaging endophenotypes are intermediate steps between the molecular and behavioural levels, and should be more easy to relate to biological processes than behavioural phenotypes.
Indeed, heritability analyses suggest that genetic factors explain a substantial proportion of the variability of various brain endophenotypes, such as regional brain volume or cortical surface area. The precise genetic causes remain, however, largely unknown. In the last 15 years, the research for these genetic causes has been tackled through the study of candidate genes and biological pathways, and more recently through agnostic genome-wide association. But the success of this objective depends also on our ability to determine and to understand the most relevant brain endophenotypes, those more closely related to the biological processes.
Here we will review the brain endophenotypes available through neuroimaging and the biological processes shape them. We will distinguish the timescales of the mechanisms of brain development, which shape our evolutionary history, and that of the individual plastic changes, which reflect our life-long experiences.

❖ Emmanuel Barillot

Tumorigenesis and tumor progression are consequences of the deregulation of molecular networks controlling essential cellular processes such as cell cycle, DNA repair, cell death or survival among others. Improving therapeutic strategies rests therefore on the understanding and modelling of these biological networks.

By analysing literature we have constructed detailed maps of these networks using systems biology standard languages. Analysis of the structure of these network allows their decomposition into functional modules and their organisation into interconnected layers.

We have then focused on the modelling of an important process which is involved in cancer : the mechanism of cell fate decision upon TNF and FAS death receptor engagement , by which a cell chooses to die by apoptosis or by necrosis, or to survive. We have conceived a mathematical model of cell fate decision, based on a logical formalisation of well-characterised molecular interactions. The dynamical modelling allowed us to analyse the temporal behaviour of a cell for different conditions, and to infer the phenotype reached (apoptosis, necrosis or survival). This was shown to recapitulate satisfactorily the experimental observation both for wild type and known mutants. The model also allows proposing prediction of mechanisms involved in the control of cell death.

❖ G. Montana

Title: Sparse regression models to detect gene effects in GWA studies of brain images

In this talk I will introduce the statistical challenges involved in neuroimaging genetics studies. I will describe a range of penalised regression models for the detections of SNPs associated to multivariate quantitative phenotypes, including models for the detection of associations with entire biological pathways. Simulation studies aimed at characterising the power of these regression methods will be presented. Finally, some results from applications to Alzheimer's disease and multiple sclerosis will be discussed.

❖ Christian Beckmann

Title: Defining phenotypes based on resting FMRI functional dynamics

I'll discuss approaches for creating resting-state fMRI derived imaging phenotypes. Further, I will provide examples of how to use these for gene association studies and extended pedigree heritability studies.

❖ E. Duchesnay

Bridging the gap between imaging and genetics: A multivariate approach based on feature selection and sparse Partial Least Squares

Brain imaging could be crucial as an intermediate phenotype to understand the complex path between genetics and behavioral or cognitive phenotypes. We propose to investigate an exploratory multivariate method in order to identify a set of Single Nucleotide Polymorphisms (SNPs) covarying with a set of brain regions. Recently, Partial Least Squares (PLS) regression has been proposed to analyze DNA and transcriptomics. However, in very high-dimensional settings like in imaging genetics studies, such multivariate methods may encounter overfitting issues. Here, we investigate the combination of a reduction dimension and a regularized version (based on the penalization of the L1 norm of model weights) of PLS to face the very high dimensionality of imaging genetics studies.