

# Progression from the mean: neuroimaging methods for modelling population variability & heterogeneity

Wednesday, Jun 20: 8:00 AM - 9:15 AM

1308

Symposium

Wednesday - Symposia AM

This symposium will highlight the importance of modelling population variability, within-group heterogeneity and individual differences when using neuroimaging data. This will be achieved by showcasing the latest data from methodological developments in the area. Much current neuroimaging research still focuses on characterising group differences using the mean and standard deviation of derived measures. Crucially, this canonical approach assumes homogeneity between members of experimental groups. This assumption is not valid for the majority of brain diseases and is likely not valid for the general population or healthy control groups. This potentially explains why quantitative neuroimaging is yet to have much clinical impact, as diseases are typically highly complex and heterogeneous, with few individuals actually resembling the 'average'. This symposium focuses on the application of different approaches to overcoming this issue, hoping to direct the progression of the neuroimaging field away from simply using the mean. The value in modelling individual differences in order to make personalised predictions, aligned with moves towards precision medicine, will be highlighted. The topic is particularly timely as the increasing amount of neuroimaging data becoming available now allows the novel application of multivariate analysis methods. For the first time, we have the opportunity to define 'normal' variability in brain structure and function in the population, thanks to initiatives such as the UK Biobank. However, unless these methodological approaches are encouraged, developed and more widely adopted, our field's dependency on measures of central tendency may remain entrenched and the chance to translate neuroimaging into clinical practice could be missed.

Objective

- Understand the limitations of using mean and standard-deviation based analyses when drawing conclusions from neuroimaging research, particularly in the context of heterogeneous brain diseases.
- Become aware of a selection of novel approaches to modelling both population variability and within-group heterogeneity using neuroimaging to overcome the limitations of case-control mean comparison analysis.
- Appreciate the importance and timeliness of further analytical developments for the translation of neuroimaging data in clinical contexts, where the goal is to make individualised predictions, particularly regarding health outcomes.

Target Audience

The methodological issues highlighted by the symposium will be of interest to anyone conducting applied neuroimaging research. These included cognitive neuroscientists interested in normal brain structure and function, alongside research focusing on clinical applications to help understand and treat brain diseases. We also hope to encourage computer scientists and mathematicians to become involved as the development of better normative models of disease will be a multi-disciplinary effort.

Organizer

*James Cole, PhD*, King's College London

## Presentations

### **The central tendency dependency: problems and potential solutions for neuroimaging research ([index.cfm?do=ev.viewEv&ev=1631](#))**

Neuroimaging, alongside many other applied fields, has long relied on statistical methods based on measures of central tendency. While this can provide useful insights into the average characteristics of groups, these average

characteristics themselves are often only useful if group members are generally similar. Here, I will discuss some of the conceptual and statistical problems with relying on group averages for our understanding of brain function and brain diseases, which are often highly heterogeneous. I will outline one possible approach to modelling individual differences, particularly relating to brain ageing, an important consideration when considering any chronic brain disease. Using a model of healthy brain ageing, I will present the results of individualised predictions of future cognitive and general health, using data from the Austrian Stroke Prevention Study, the Lothian Birth Cohort 1936 and in the context of multiple sclerosis.

Presenter

*James Cole, PhD, King's College London*

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## **Identifying neurodegenerative disease subtypes and their temporal progression using Subtype and Stage Inference ([index.cfm?do=ev.viewEv&ev=1632](#))**

Although the neuropathology of many neurodegenerative diseases has been shown to be highly heterogeneous, the majority of studies continue to analyse each neurodegenerative disease as a single group at a single disease stage (e.g., mild, moderate and severely affected). This conflation of disease subtypes and disease stages potentially contributes to the high failure rate of clinical trials in dementia, through an inability to identify distinct subgroups of individuals that may benefit from distinct treatments. I will present Subtype and Stage Inference (SuStaln): a novel machine-learning tool able to identify subgroups of individuals with distinct temporal progression of neurodegeneration on MRI. We demonstrate the utility of SuStaln in two neurodegenerative diseases: genetic Frontotemporal dementia (FTD) and Alzheimer's disease (AD). Results reveal new within-genotype subtypes in genetic FTD, and characterise the temporal progression of AD subtypes in previously unseen detail. The SuStaln subtypes and stages are able to distinguish genotype with high classification accuracy in genetic FTD, and significantly enhance the ability to predict conversion between diagnostic categories in AD. SuStaln is broadly applicable across a range of diseases and to non-imaging markers.

Presenter

*Alexandra Young, PhD, University College London*

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## **Brain Aging Heterogeneity with Machine Learning: dimensional multi-site neuroimaging reference system ([index.cfm?do=ev.viewEv&ev=1633](#))**

Brain aging is associated with highly heterogeneous and frequently overlapping clinical phenotypes, leading to challenges in differential diagnostics in the presence of pre-clinical neurodegenerative disorders. Previous neuroimaging and machine learning work has produced brain signatures that could capture brain structural changes, however heterogeneity within broad disease groups has been largely ignored. Recent imaging advances offer novel opportunities to investigate a multitude of brain changes with aging and related neurodegenerative disorders, including Alzheimer's. I will present data on our research using machine learning with neuroimaging data to establish multi-dimensional multi-modal normative curves of brain aging, by leveraging data obtained from a consortium of several large studies (including ADNI, the Baltimore Longitudinal Study of Aging, the Study of Health In Pomerania). Our goal is to identify dimensions of brain aging that establish a reference for diagnoses, and demonstrate relationship to normal and pathological brain aging. We will present new data from multi-site imaging studies of N>6000, where we examined diverse aspects of the heterogeneity in brain aging using advanced machine-learning methods to predict diagnosis and prognosis. We will demonstrate the challenges of multi-site harmonization and validation in addition to state-of-the-art solutions of those challenges as we move towards precision medicine.

Presenter

*Mohamad Habes, PhD, University of Pennsylvania*

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## **Structural Brain Alterations in Depression Based on Individual Deviations from Normative Age-Related Patterns of Brain Structure ([index.cfm?do=ev.viewEv&ev=1634](#))**

Major depressive disorder (MDD) is a complex and heterogeneous mental disorder that dynamically affects the brain depending on stage of life and stage of illness. Identifying brain alterations as individual deviations from normative patterns of brain development, instead of examining mean differences in the entire group of patients, can provide new insights into the heterogeneous patterns of brain abnormalities observed in MDD. I will present normative models estimated using data from healthy controls as part of the ENIGMA MDD consortium (N=4,000). We mapped the association between age and brain structure, analogous to defining 'growth curves' that track child development in terms of height and weight as a function of age. We subsequently applied these normative model parameters to MDD patients (N=3,200) to obtain predicted brain values and Z-scores that quantify the difference between predictive and true brain values measures, representing an individual patient's deviation from the normative range at their age. Clustering analysis identified different subgroups of patients with unique patterns of structural brain alterations, thereby reducing neurobiological heterogeneity within MDD. The impact of different machine learning methods and potential confounding effects including scan site will be discussed.

Presenter

*Lianne Schmaal, PhD, University of Melbourne*

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