Charting brain variability in health and disease using normative models

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Overview

Normative models ("brain charts") are emerging as a highly promising approach to understand variation in large population-based cohorts and to make statistical predictions at the level of the individual in an analogous manner to growth charts in pediatric medicine (Marquand et al. 2016). They are now widely used to precisely quantify brain development and ageing across the lifespan (Ziegler et al. 2014; Bethlehem et al. 2021; Rutherford et al. 2021) and to parse the heterogeneity in many clinical conditions including preterm birth (O'Muircheartaigh et al. 2020), cognitive impairment/dementia (Habes et al. 2021), autism (Zabihi et al. 2019), schizophrenia (Wolfers et al. 2018) and attention deficit/hyperactivity disorder (Wolfers et al. 2020). In this symposium, we will give a conceptual overview of this modelling paradigm and will discuss the ability of normative models to move beyond classical group comparisons towards understanding individual differences with respect to a common reference model. We will describe state-of-the-art machine learning approaches that underpin normative modelling, highlight methodological and interpretational challenges they entail such as the necessity of estimating these models on large population-level cohorts, dealing adequately with structured variation in the data (e.g. due to scanner site) and properly interpreting the deviations that result from these models. We will outline recently developed solutions for practitioners in the neuroimaging field and highlight novel clinical applications of normative modelling in multiple domains.

Lecture 1: *Shifting the focus from the population to the individual*

Andre Marquand, PhD Presenter

In this talk I will provide a conceptual perspective to outline the fundamental differences between normative models and classical approaches that focus on detecting group differences. I will show how normative models can provide a useful platform for individualised prediction, cohort stratification, the

ability to align heterogeneous data to a common reference and facilitate quantitive inferences about patterns of similarity and difference across individuals. I will describe different methodological innovations that we and others have developed for accurately modelling population variation and to provide individualised fingerprints that can be used for stratifying cohorts and predicting individual differences, including extreme value statistics and latent variable models. I will illustrate this discussion by highlighting several applications that show the use of normative models in understanding population variation in imaging-derived phenotypes across the lifespan and for parsing the heterogeneity of disorders such as autism and schizophrenia.

Lecture 2: *A Normative modelling approach to accommodate site effects in multi-site neuroimaging studies*
Johanna Bayer Presenter

Recent years have seen a trend towards creating large neuroimaging data sets by pooling existing data, with the aim to increase statistical power and obtain more reliable estimates of effect sizes. However, a major disadvantage in this approach is the presence of confounding "scanner effects" (Fortin et al., 2017, 2018, e.g., differences in field strength, scanner manufacturer etc. (Han et al., 2006). These confounding effects present as site correlated biases that cannot be explained by biological heterogeneity between samples. Instead result from a potentially complex interaction between site and variables of interest, and thus cannot easily be estimated or removed. In this talk, I will show that site effects on cortical thickness data can be accommodated for by including the site effect as predictor in a normative model.
We compared the performance of a linear and a non-linear normative model based on hierarchical Bayesian regression in modeling the effect of age on cortical thickness in their ability to correct for site effects. We used data of 570 healthy individuals from the ABIDE (autism brain imaging data exchange) data set in our experiments. In addition, we used data from individuals with autism to test whether our models are able to retain clinically useful information while removing site effects.
We compared the proposed single stage hierarchical Bayesian normative modelling method to several harmonization techniques commonly used to deal with additive and multiplicative site effects using a two-stage regression, including regressing out site and harmonizing for site with ComBat, both with and without explicitly preserving variance related to age and sex as biological variation of interest. In addition, we made predictions from raw data, in which site has not been accommodated for.
I will show that the normative method based on hierarchical Bayesian regression showed the best predictive performance according to multiple metrics compared to other methods. In addition, the z-scores resulting from the normative model showed little to no residual site effects, yet still retained clinically useful information.
Our results show the value of normative modelling methods for accommodating site variation in neuroimaging data, which provides an alternative to harmonization techniques.

Lecture 3: *Disentangling clinical and biological heterogeneity in depression*
Janine Bijsterbosch Presenter

In this talk I will discuss a recent application of normative modeling to investigate heterogeneity in depression. Importantly, heterogeneity can take the form of individual differences in clinical presentation (e.g., symptoms, age of onset, number of episodes, etc.) and/or in biological factors (e.g., brain mechanisms). In this study we used normative modeling in the UK Biobank to obtain normative deviations of imaging derived phenotypes in depressed individuals as compared to a healthy comparison

cohort. We defined multiple clinically homogeneous groups by identifying individuals high in one symptom of depression but low in other symptoms. This isolation of clinical factors (that are often highly colinear) was uniquely enabled by the UK Biobank population sample. Normative deviations were used to investigate differential brain patterns across clinically homogeneous groups. Subsequently, data-driven subtyping based on normative deviations was performed separately within each clinically homogeneous group. The results revealed highly stable biological subtypes after tightly controlling for clinical heterogeneity. As such, this study illustrates the value of normative modeling and provides example uses of normative deviations in both hypothesis-driven and data-driven follow-up analyses.

Lecture 4: *Brain aging charts: neuroimaging and machine learning define normative trajectories*
Mohamad Habes, PhD Presenter

In this talk I will discuss state-of-the-art neuroimage harmonization and Artificial Intelligence (AI) methods to construct a Brain Chart of early signatures of brain aging, Alzheimer's disease (AD), and white matter disease in a diverse consortium with more than ten thousand MRI scans and a dozen of cohort-based studies. The developed signatures provide an excellent example of the use of non-invasive tools, such as magnetic resonance imaging (MRI), for high-quality early detection of abnormal or declining brain function. The brain aging signature predicts the brain age (as opposed to chronological age) of an individual from MRI data, which enabled exploration of the heterogeneity through deviation from normative brain aging trajectories and defining brain resilience vs. susceptibility to neurodegeneration. Our study investigates associations of these signatures with cognition and amyloid-beta (Aβ) deposition and reveals early age associations between small vessel ischemic disease and brain aging, lower cognition, and AD neuropathology, potentially indicating an early role of white matter disease in AD. Associations between resilient brain aging and preservation of cognition were also found. This Brain Chart provides personalized predictions of individuals' brain aging-, AD- and white matter disease patterns. It develops a precision medicine approach for characterizing the heterogeneity of brain aging and dementia, which may permit personalized risk prediction and targeted treatment trials.