One-shot normative modelling of whole-brain functional connectivity | Janus Rønn Lind Kobbersmed

Many brain diseases and disorders lack objective measures of brain function as indicators of pathology. The search for brain function biomarkers is complicated by the fact that these conditions are often heterogenous and described as a spectrum from normal to abnormal rather than a sick-healthy dichotomy. As a response to this issue, normative modelling has emerged to characterize the normal variation of brain measurements given sex and age. Abnormalities are then identified as deviations from the distribution of normal brain measures. In fMRI studies, brain function is often assessed as functional connectivity (FC), which is calculated as the correlation matrix of activity between pairs of brain regions or networks. Normative modelling of FC requires a large, healthy population and a method to predict FC from sex and age. However, predicting FC is challenging because of its mathematical structure and high dimensionality. Current normative modelling studies have mainly focused on predicting the pairwise FC (i.e. correlation coefficients) individually rather than the full FC (correlation) matrix, thereby ignoring its semi-positive definiteness and generating a large number of hypotheses. Here, motivated by the fact that brain diseases often affect the interplay between multiple brain regions, rather than properties of isolated pairs, we adapt a newly developed method from the statistics literature for the needs of normative modelling, so that we can find linear projections of FC matrices based on sex and age. Using this new approach, which we termed Functional Connectivity Integrative Normative Modelling (FUNCOIN), and resting-state fMRI data from the UK Biobank, we propose a normative model based on whole-brain FC by identifying two sex- and age-dependent projections, which successfully characterize the normal range of functional connectivity. By modelling the entire brain at once, FUNCOIN allows for identifying network-level changes associated with sex and age which traditional elementwise methods cannot reveal. This way, we found that subjects with Parkinson's disease were significantly, and substantially, more likely than healthy subjects to exhibit an abnormal pattern of FC even on scans up to 5.5 years before being diagnosed.

Authors: Janus R. L. Kobbersmeda (Aarhus University), Chetan Gohil (University of Oxford), Andre Marquand (Radboud University), Diego Vidaurre (Aarhus University)