

Connectivity Studies in Large Populations: Towards Defining Disease Mechanisms & Risk

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It now is well recognised that MRI methods provide powerful measures for precise phenotypic that can be applied to elucidate markers of disease or disease risk. Building on advances in automated quantitative analyses, large scale imaging studies have now been developed in a number of collaborations to inform biomarker development, characterisation of disease course and more fundamental epidemiological investigations. These have enabled imaging data to be integrated with a broad range of clinically-relevant and demographics measures to discover and validate imaging markers.

The latest of these studies to be funded is the most ambitious to date: the UK Biobank Imaging Enhancement. UK Biobank (www.ukbiobank.ac.uk/) is a large prospective cohort that was established by the Medical Research Council and Wellcome Trust as a resource for the investigation of risk factors for major diseases and morbidities of middle and older age. 500,000 men and women aged 40-69 years were recruited nationwide between 2006 and 2010. The baseline assessment was extensive, with detailed information gathered on prevalent disease, diet, lifestyle, socioeconomic factors, education, medications/ supplements (by questionnaire) and specific measurements such as blood pressure, weight, height, bio-impedance, grip strength and ultrasound measures of heel bone density. Venous blood samples were collected, including DNA, and results of a panel of standard biochemical, haematological and immunological assays which are likely to be of interest to a wide range of researchers, along with chip-based genotyping data (to become available during 2014-15). Large subsets of the full cohort have undergone additional investigations such as retinal imaging by optical coherence tomography and objective physical fitness and activity monitoring. The baseline assessment is being repeated every few years in subsets of about 20,000 participants to enable calibration of measurements, adjustment for regression dilution and estimation of longitudinal change. The UK Biobank database is linked with NHS information systems in order to capture data relating to incident disease outcomes. UK Biobank combines unprecedented size, breadth and depth for a prospective longitudinal cohort study. As incident cases accrue, it will allow musculoskeletal health outcomes to be related to a uniquely broad range of risk factors through case-control studies nested within the overall cohort.

Toward the end of 2012, funding for the pilot stage of the Imaging Enhancement was secured from MRC/ Wellcome, which will allow detailed imaging acquisition on 6-8,000 volunteers from the original UK Biobank cohort to commence in late 2013. This comprehensive imaging assessment will include 3T MRI of the brain including advanced DTI and resting state fMRI for connectivity analysis; 1.5T MRI of the heart and upper abdomen; Carotid Doppler; DXA of whole body, lumbar spine, hips, together with vertebral fracture assessment and imaging of both hips and knees; subject to successful completion of the pilot, the intention is to extend to a total of 100,000 participants across England. This enhancement will also include a repeat of most of the baseline assessment, including cognitive assessments. This breadth of phenotypic information in such a large cohort will yield a unique opportunity to apply MRI in the context of other techniques to investigate risk factors for disease both within and across organ systems.

The development of the UK Biobank Imaging Enhancement represents an expansion of an exciting new type of imaging science based on work developed by a community committed to creation of an open resource, accessible to researchers world-wide for the broadest range of relevant work. Large scale imaging of this type of course of course poses unique logistical, ethical and analytical challenges that will need to be solved by the community working together, as well. However, the great success of similar, smaller approaches such as ADNI promises that benefits can be felt widely. The unique availability of high quality DTI and resting state fMRI data will help to move connectivity studies from disease association to disease risk assessment.

Large scale imaging studies and epidemiological application and progress towards realisation of the UK Biobank Imaging Enhancement objectives of applying brain connectivity measures on a similar scale will be reviewed in an effort to encourage wider debate of major issues and engagement with this exciting effort.