Imaging in large populations: better defining later life brain disease risks using brain connectivity

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This lecture will review the application of imaging connectivity measures in disease epidemiology, challenges to the implementation of advanced imaging in large scale studies and the great promise that connectomics-based imaging epidemiology offers for defining new risk factors for brain disease.

It now is well recognised that MRI methods provide powerful measures for precise phenotypic characterisation that can be applied to discover markers of disease or disease risk factors. Building on advances in automated quantitative analyses, large scale imaging studies have now been developed in a number of collaborations (e.g., ADNI, http://www.adni-info.org/) and already have contributed substantially to biomarker discovery, characterisation of disease course and more fundamental epidemiological investigations. Together, these developments are creating a new "imaging epidemiology".

The latest of these studies to be funded is the most ambitious to date. It is being developed within the UK Biobank (www.ukbiobank.ac.uk/), a large prospective cohort that was established by the UK 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 and specific measurements such as blood pressure, weight, height, bio-impedance, grip strength and ultrasound measures of heel bone density and cognitive testing. Venous blood samples were collected 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 will be available soon, along with chip-based genotyping data (to become available in 2015). 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 by remote accelerometry. The baseline assessment is being repeated every few years in subsets of approximately 20,000 participants to enable calibration of measurements, adjustment for regression dilution and estimation of longitudinal change. The UK Biobank database is linked with UK National Health Service information systems in order to capture data relating to incident disease outcomes.

The UK Biobank thus combines what for its time was an unprecedented size (similar efforts have been developed in China and elsewhere), breadth and depth for a prospective longitudinal cohort study. As incident cases accrue, it will allow a broad range of health outcomes- particularly including those for late life brain diseases- to be related to a uniquely broad range of risk factors through case-control studies "nested" within the overall cohort.   This highlights a special feature of the *longitudinal* design from enrolment to death: the epidemiological value rises with time as health outcomes for the participants are expressed.

Toward the end of 2012, funding for the UK Biobank Imaging Enhancement was secured from the UK Medical Research Council and the Wellcome Trust. The objective of the Imaging Enhancement is to provide a comprehensive imaging assessment that 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 and DEXA of whole body, on a total of 100,000 participants across England. The first stage of the project- to be conducted over 2014-15-   will be to optimise processes, explore ethical issues and evaluate the feasibility of this complex, high throughput imaging. Subject to success in demonstrating these, the full programme is expected to be initiated from 2015-16. The 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 large size of the cohort was based on statistical power calculations for nested case-control studies, showing that 5-10,000 cases of any particular condition would be required for the reliable detection of odds ratios (ORs) of 1.3-1.5 for the main effects of different exposures (the upper end of the range reported from genome-wide association studies of various conditions), and around 20,000 cases for interactive ORs of 2.0 or more. The objective is not to use the resource in a single investigation, but to enable the generation of nested case-control studies, each of which is individually powered to address an important question.

Large scale imaging of this type of course poses unique logistical, ethical and analytical challenges. One of the most complex issues for the project to address is the approach to management of unexpected, abnormal findings on images. A pragmatic approach provisionally adopted by UK Biobank, which has been very carefully reviewed, taking into account evidence from literature reviews, experiences from other population imaging research projects, discussions with the Royal College of Radiologists and the Society and College of Radiographers and legal advice is that only limited feedback for unexpected findings considered to be potentially 'serious' (defined in this context as likely to threaten life span, quality of life or major body functions) that are observed incidentally (i.e., not as part of a formal clinical screening process) during data acquisition or quality control will be provided to participants. This will be done by having radiographers "flag" potentially abnormal scans (e.g., those with brain tumours, vascular malformations, aneurysms), which then will be reviewed by a radiologist. Subsequently, if appropriate (i.e., clinically meaningful and potentially actionable), feedback will be provided to the participant and his or her doctor. This approach to incidental findings in the Imaging Enhancement is consistent with the standard operating procedure on incidental findings that already has been used previously in UK Biobank for assessments conducted on the 500,000 participants to date. Participants will be given detailed and explicit information about the procedures they will undergo during the imaging assessment (including the approach to feedback of incidental findings) before giving consent. A key aspect of the first year of optimisation and feasibility study preceding a final decision to move towards the full protocol will be evaluation of participant understanding of the UK Biobank's approach and its impact on them and the wider health community.

The related research scope was further expanded in October 2013 with new MRC funding for Phase I of the UK Dementia Platform (DP), the mission of which is to integrate UK population cohorts to develop a new resource for research intended to prevent the onset, and delay the progression, of neurodegenerative diseases. DP will create a common bioinformatics framework and access portal to include UK Biobank, the Imaging Enhancement population and those of other UK large epidemiological cohorts to allow study of late life dementia and its risk factors from birth to death. As part of this effort, additional follow up imaging, including PET, as well as MRI, will be conducted on the UK Biobank Imaging Enhancement population, as well as additional evaluations, such as extensive and frequent blood and CSF biomarker evaluations and serial cognitive testing. A subset of the population will be asked to volunteer for re-contact for experimental medicine studies in an effort to pioneer a new approach to lowering the cost and other barriers to development of novel therapeutics.

An important aspect of UK Biobank is that it has been developed by a broad community working together. It was established and is now being enhanced as a result of the altruism and generosity of its participants, the long-term vision of its major funders, an approach involving streamlined governance, centralised infrastructure, "industrial" methods for collection and processing of data and samples, effective working between academic and management disciplines, and widespread public support. What is very special is the resolute focus is on encouraging extensive use of the resource, which will become available to the *international* research community without preferential or exclusive access.

With achievement of the first objectives of the UK Biobank Imaging Enhancement and the UK Dementia Platform underway, large volumes high quality DTI and resting state fMRI data will become available to researchers world-wide to help to move connectivity studies from disease association to disease risk assessment.