Imaging in large populations: better defining later life brain disease risks in terms of development, exposure and aging

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Imaging, family history, genetics, lifestyle and exposure data promise new opportunities for understanding disease risk as an integrated outcome of developmental factors and environment. New capabilities applied at large scale are offering an unprecedented opportunity to address this challenge.

One of the most recent of these studies 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. Biomarker and genetic data also are avalaible. Longitudinal follow up to death will continue with linkage to medical records.

The UK Biobank thus combines great size, breadth and depth for a prospective longitudinal cohort study. As incident cases accrue, it allows 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.

Last year, the UK Biobank Imaging Enhancement was initiated with funding 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. During the first year, processes have been optimised ethical issues explored and the feasibility of this complex, high throughput imaging demonstrated.

For my group, this resource will enable investigations of brain disease based on genetic and observations of longitudinal changes in probands, along with observations of *forme fruste* of disease across clinically healthy individuals sharing risk factors. One area of focus will be further testing of the hypothesis that healthy age-related brain degeneration mirrors development, with the areas of the brain thought to develop later also degenerating earlier. To illustrate how such large imaging datasets can be used, I will review a pilot study of 484 healthy subjects that revealed a transmodal network, the lifespan pattern of age-related changes in which highlighted ways in aging is related to the patterns of development of the brain. This work provided evidence that the network of brain regions which develops relatively late during adolescence shows accelerated degeneration in old age compared with the rest of the brain and is characterized by areas of heightened vulnerability to unhealthy developmental and aging processes. This link between development, processes of aging and cognitive outcomes provides a broad framework for consideration of many diseases of the brain. Availability of large imaging datasets from UK Biobank and similar initiatives in the near future should enable powerful explorations of this to be undertaken.

References

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