MRI at UK Biobank

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Introduction

UK Biobank is a large prospective cohort study designed to understand the causes of common chronic disease with the aim of improving the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression, and forms of dementia. UK Biobank recruited 500,000 people aged between 40–69 years in 2006–2010 from across Great Britain to take part in this project. They have undergone a range of physical measures, provided detailed information about themselves, and have given blood, urine, and saliva samples for future analysis. Also, participants agreed to have their health followed throughout their lives through linkage to their medical records. This will help scientists clarify why some people develop particular diseases and others do not.

In 2012, a proposal for an imaging enhancement in 100,000 participants was made to quantify detailed phenotypes that may be associated with disease and enhance the power to detect associations with incident health outcomes. The simultaneous imaging of brain, heart, arteries, abdomen, and bone in each individual participating in the imaging enhancement and the combination of these data would provide a dataset that is uniquely able to allow questions to be addressed regarding the relationships between phenotypes across organ systems and allowing assessment of pathophysiological mechanisms operating at a systemic level. For example, the relationships between obesity and aging-related macrostructural brain changes with later-life cognitive dysfunction [1] may suggest specific mechanisms and associations with incident disease and need further exploration in much larger datasets. Such correlations, which are based on prevalent disease, also need to be extended to studies of the associations of pre-symptomatic measures of body phenotype (e.g. body MRI and dual-energy X-ray absorptiometry (DXA)) with future brain health outcomes. The potential to relate longer term clinical and cognitive dysfunction outcomes to sensitive brain structural and functional markers, cardiac and body composition phenotypes (as well as to information on blood markers, lifestyle, and clinical history) would allow new depths of exploration of risk and pathogenic mechanisms, and the generation of new hypotheses regarding possible modifying factors. In the shorter term, value of the imaging enhancements in UK Biobank can be realised through cross-sectional case-control studies, e.g., relating brain imaging differences to prevalent brain disease or to independent phenotypic measures.

The pilot phase of imaging 5,500 participants was completed in September 2015. Further funding allowed for the main phase to start in 2016. In total, over 14,000 participants have already been scanned and imaging data from 10,000 subjects has been released for use by the international research community (http://www.ukbiobank.ac.uk/2017/02/new-data-from-brain-imaging-and-on-heart-attacks-and-strokes-available/). As many as 100 research groups are accessing the imaging data for their research.

The imaging methods employed are: magnetic resonance imaging (MRI), carotid ultrasound, and dual-energy X-ray absorptiometry. For MRI, three specific areas of interest were identified: brain, heart, and body imaging. The specifics of each MR application are described in the following sections.

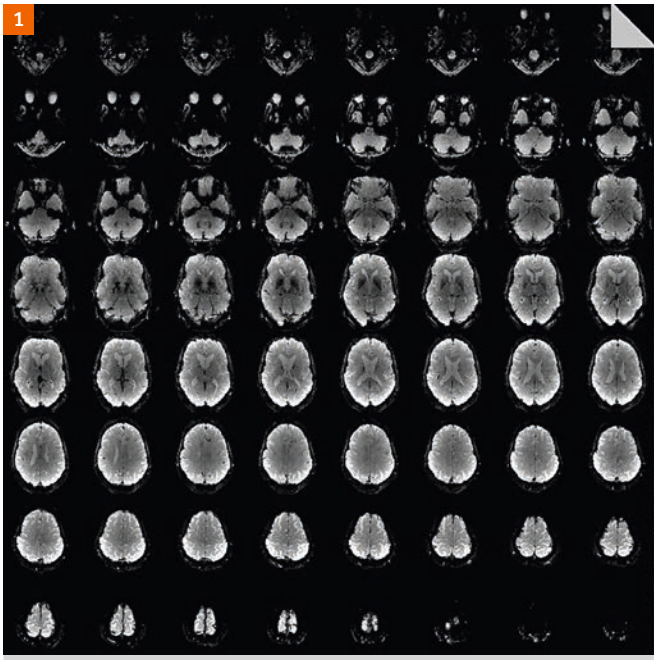

Figure 1: fMRI time point with simultaneous excitation of 8 slices.

MR imaging

To meet the temporal, financial, and geographic constraints of scanning 100,000 participants, the measurements are made in three different locations each fitted with two scanners (one 3T MAGNETOM Skyra and one 1.5T MAGNETOM Aera). Scanning sites were selected to allow maximize volunteer recruitment from UK Biobank participants across the UK. Currently, the primary site in Stockport, near Manchester, UK, is running with an average of 17 participants scanned per day (strictly within 12 h) on 7 days per week. The second site in Newcastle, UK, will be operational in April 2017 using the identical software and protocols. A third site in Reading, UK, will receive participants at the end of 2017. The brain program runs for about 30 minutes exclusively on the 3T systems, while an integrated body and cardiac program is measured on the 1.5T scanners for 10 and 20 minutes, respectively.

Major challenges, as one might expect, centre on the selection of the specific applications within each body region, the choice of measurement techniques, and the setting of protocol parameters. The need for data harmonization means that these decisions, which were made based on experience in the pilot phase, will be applied for all data acquisition in the next phase of development of the resource. Many developers and subject matter experts worldwide have contributed to the selection and optimization of the final imaging sequences and data management. An externally chaired imaging working group (constituted from leading UK academic researchers in relevant areas) has been responsible for the design of the imaging enhancements. Pre-piloting the feasibility of the proposed imaging protocols for each of the separate elements of the imaging assessment visit informed the final program further. There has also been careful consideration and consultation on the issue of providing feedback on incidental findings from imaging, including the implementation of a prospective study of unexpected findings of potential medical significance and both their clinical consequences and impact on lives of the volunteers affected.

Considerable effort within and outside Biobank is devoted to data transfer and security. This includes the encoding and separation of personal information to allow complete DICOM streams to be provided.

Along with the protocol for examinations, a quality assurance procedure was developed. There are three different quality aspects to consider over time: the status of the scanners, the actual scanning of participants, and the evaluation of data. The first aspect is realized by a regular high resolution phantom scan which detects B_0 and B_1 variations of the hardware as early as possible. Close cooperation with the service department is important in order to resolve potential issues as fast as possible and the proactive effort of the service employees is much appreciated. The second aspect requires the active participation of radiographers in an unconventional way. The scan protocol must change as little as possible while the circumstances and constancy of parameters must be checked as often as possible. While the orientation and position of an oblique protocol is slightly adjusted to the tilt of the head, none of the other scan parameters are modified. This also means, for example, that exactly 6 stages for the complete body are scanned irrespective of the height of the participant. This is a consequence of the decisions to keep both the measurement and acquisition time fixed. Hence, one must not underestimate the role of education and the challenges of an environment where the creative optimization and adjustment of protocols to the subject are neither desirable nor permitted. Tools are currently being developed to provide automatic checks against constancy of relevant parameters. The third aspect requires an evaluation of the resulting scans via the review of a number of defined image parameters. This depends on the evaluation chain of developers and it is important to establish a close feedback process.

Brain imaging

The brain MRI protocol will provide researchers with data concerning both brain structure and function from a single, short examination, including data to reconstruct the major white matter connection pathways. Each participant undergoes a 32-minute brain MRI protocol using a 3 Tesla MAGNETOM Skyra. This provides T1- and T2-weighted FLAIR structural 3D MRI, functional MRI during rest and task performance, whole-brain diffusion tensor imaging, susceptibility-weighted imaging (SWI), and arterial spin labeling (ASL).

The brain program comprises the following protocols:

- AutoAlign Scout images
- T1-weighted structural morphology MPRAGE with iPAT 2
- fMRI resting state protocol with simultaneous excitation of 8 slices
- fMRI task performance protocol with simultaneous excitation of 8 slices
- T2-weighted 3D FLAIR with iPAT 2
- Diffusion AP b = 0, b = 2 ms/μm^2 with 6 directions and simultaneous excitation of 3 slices
- Diffusion PA b = 0, 104 directions in total distributed over two shells with b = 1 and 2 ms/μm^2 with simultaneous excitation of 3 slices
- 3D SWI iPAT 2
- 3D pcASL

Highly efficient scanning protocols are needed to allow the full range of imaging and other phenotype measures to be obtained on each volunteer. To perform this imaging program within the limited time allocated, the use of acceleration techniques, in particular the simultaneous excitation of multiple slices, is required. It is also apparent

that the acquisition of data is tuned to the minimum required while the data quality and contrast aims to be the best per unit time of acquisition.

Cardiac imaging

Cardiovascular MRI is considered the most versatile and precise technique for simultaneous assessment of multiple cardiac parameters. Its reproducibility and non-invasiveness are key advantages for large-scale population studies over other imaging modalities such as echocardiography. An additional attractive feature for large scale population studies is that volunteers are not subjected to any potentially harmful radiation (as with cardiac CT). A major strength of CMR is the ability to obtain multi-parametric images in one imaging session related to both structure and function of the heart. A 20-minute protocol using a 1.5 Tesla scanner provides time-dependent heart chamber volumes, cardiac wall thickness and mass, tissue motion using tagging, and aortic size and compliance. In addition, the aortic flow quantitation is performed and the myocardial T1 is estimated.

The cardiovascular program consists of the following protocols:

- Cine scanning of the left ventricular long and short axis views
- Cine scan of the left ventricular outflow tract with ascending aorta
- Cine tagging of 3 short axis planes around the middle of the left ventricle
- Cine cross section of ascending aorta and proximal descending aorta
- Through-plane flow measurement of ascending aorta
- T1 mapping of mid-ventricular slice

Body imaging

There are a number of methods for estimating body fat content (such as the BMI, waist-hip circumference, and bio-impedance measures already included in UK Biobank). However, such estimates are imprecise (although still have predictive power) and cannot be used to assess adipose tissue distribution, which is both an individually distinctive phenotype and a determinant of relative disease risk. MRI can provide much more accurate information on fat content and distribution, muscle mass, and organ volume. A wide variation has been found between individuals in the amount of visceral, muscle, and liver fat for any given body mass index (BMI), waist-to-hip ratio (WHR), and total amount of body fat [5]. There is increasing evidence to suggest that fat distribution, rather than amount of fat, is important for determining an individual's risk of future disease [2, 3]. Body MRI provides an opportunity to examine the predictive importance of particular fat deposits (visceral, liver and pancreas) and the relative distribution of fat for the development of particular conditions (e.g. vascular disease, diabetes, and certain types of cancer). The 10-minute protocol on a 1.5 Tesla scanner provides quantitative information on subcutaneous-abdominal and visceral adipose tissue volumes and distribution and on intra-hepatocellular and intra-pancreatic lipid.

The body program comprises the following protocols:

- Dixon imaging of 6 contiguous stages beginning from neck downwards to the knees
- T1-weighted VIBE of pancreas

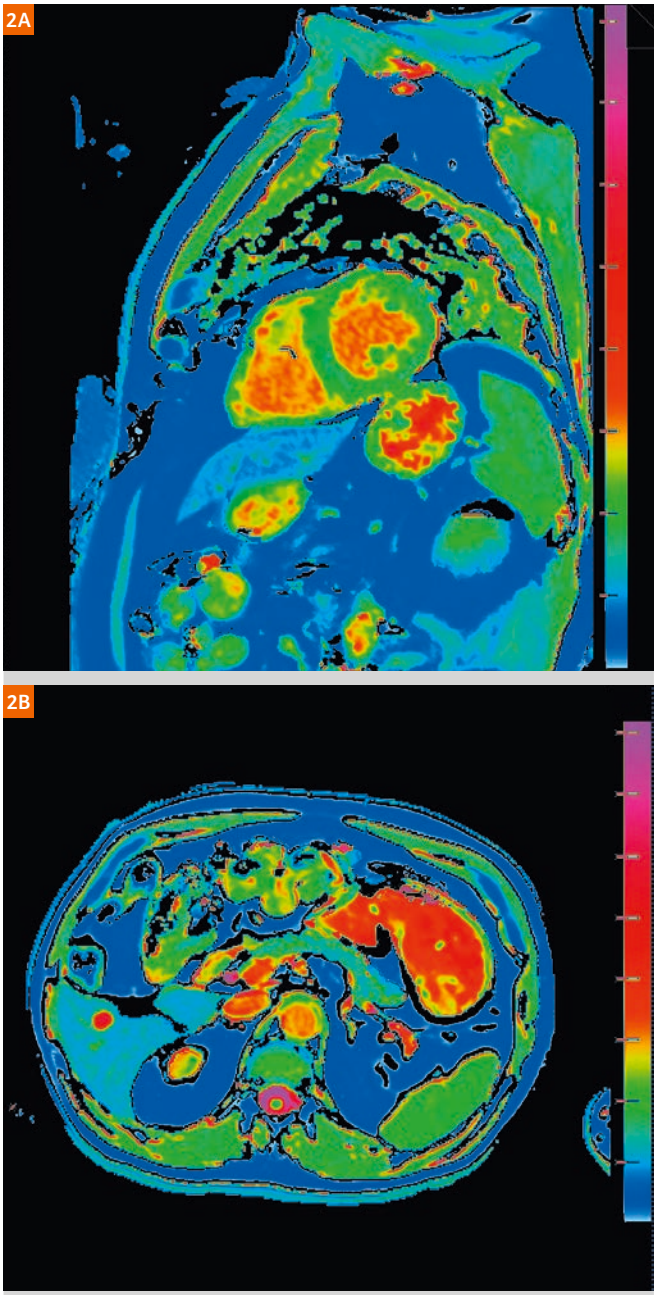

Figure 2: Computed T1 maps of heart and pancreas after acquisition of shMOLLI.

- T1 mapping of mid-liver axial cross-section
- T2*-weighted multi-echo imaging of liver cross-section
- T1-mapping of pancreas cross-section
- T2*-weighted multi-echo imaging of pancreas cross-section

Summary

The multi-modal imaging enhancement of 100,000 UK Biobank participants is well underway. This brief article presents an overview of the measurements within 1 hour of scan time with excellent quality. This, however, requires a strict regime of timing and scheduling to be performed successfully. UK Biobank solved a variety of challenges related to the infrastructure and logistics of the daily throughput. We would like to further stimulate the interest of researchers in using the unique dataset for research for many years to come. It is our hope that the community finds the data (depth, breadth, and quality) useful in answering a range of research questions.

The data and information UK Biobank presents is the result of the work of many people. The developers who programmed the sequences and those who provided the programming environment in the first place are as important as the final authors of the research publications that make use of the measurements. The insight and vision of funders provide a sound backbone of the activities of the many different departments of UK Biobank; MR images are now an exciting part of the growing data set within the UK Biobank data repository. We would like to thank and acknowledge the many contributors to this work inside and outside of UK Biobank. Specifically the use of the multiband implementation from CMRR (University of Minnesota) and the pcASL sequence from Fraunhofer MEVIS are acknowledged.

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Further information

A primary portal for information on UK Biobank and how to access the data, which is available for all researchers, is:	www.ukbiobank.ac.uk/
In 2016, several milestones were achieved. Together, these describe the developing resource well:	www.ukbiobank.ac.uk/2016/11/scanning-study-launched/ www.ukbiobank.ac.uk/2016/09/brain-imaging-results-from-5000-subjects/ www.ukbiobank.ac.uk/2016/03/uk-biobank-looking-at-the-whole-person
Reports presented in annual UK Biobank meeting (2016) can be accessed through:	www.ukbiobank.ac.uk/listen-again-annual-meetings/
The actual publications can be found easily with a specific search term, for example, the cardiac, abdominal, and neuro publications, respectively, are listed here:	www.ukbiobank.ac.uk/published-papers/?tps=cardiac&tps_button=Search www.ukbiobank.ac.uk/published-papers/?tps=body&tps_button=Search www.ukbiobank.ac.uk/published-papers/?tps=neuro&tps_button=Search
Information on how to access the DICOM data and how to apply for downloading keys can be found at:	www.ukbiobank.ac.uk/register-apply/

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