Discovery Award – Dr Ludovica Griffanti

Harmonising large-scale imaging databases to provide integrated assessments of the role of white matter hyperintensities in cognitive ageing

Objective(s):

Image characteristics of MRI datasets vary considerably across studies, causing imaging-derived measurements not to be directly comparable. This hinders the possibility of successfully exploiting the increasing availability of large neuroimaging datasets. Harmonisation aims to remove non-biological differences across datasets, producing consistent measurements. Data can then be pooled to increase the statistical power of research studies, or can be used to generate normative distributions of neuroimaging markers, improving their clinical utility. The aim of this Discovery Award was to harmonise measurements of white matter hyperintensities (WMH) in existing DPUK cohorts. Alongside grey matter structural changes (e.g. reduced hippocampal volume), WMH are known to be linked to cognitive decline and diseases of ageing. WMH measurements could therefore play an important role in predictive imaging-derived risk scores for future cognitive impairment and neurological diseases.

The specific project aims were:
1. Analysis of the distributions of white matter hyperintensities (WMH) in the available datasets to identify sources of difference.
2. Development and testing of harmonisation procedures
3. Harmonised WMH measures and harmonisation tools available on the DPUK portal

Overview Summary:

This project arose from a DPUK Discovery Award to Dr Ludovica Griffanti who is based at the University of Oxford. Dr Griffanti aimed to find methods to compare large sets of brain magnetic resonance imaging data. This is needed because there are some small but important changes in the way that brain images are captured by different scanners and 'removing' these differences is important to allow datasets to be compared and combined. In this way research findings could be confirmed on larger numbers enhancing statistical significance and, ultimately, individual scans could be compared to a reference dataset, improving the accuracy of diagnosis. In particular, she studied White Matter Hyperintensities (WMH), brain changes that are known to be linked to cognitive decline and diseases of ageing. Two major studies of elderly populations (Whitehall II imaging sub-study and UK Biobank) were used. The work showed that, by using specific, standardised analysis techniques and by taking into account the biological differences of the populations (e.g. age), it was indeed possible to derive comparable WMH measures from the datasets.

The results open up a number of avenues for studies suggesting it is feasible to study WMH and other neuroimaging markers across extensive clinical databases.

Executive Summary:

Large scale neuroimaging datasets present the possibility of providing normative distributions of a huge variety of neuroimaging markers, which would vastly improve the clinical utility of these measures. However, a major challenge is our current poor ability to integrate measures across different large-scale datasets. This is due to uncertainties about the consistency of imaging and non-imaging measures across the different protocols and populations.

This award explored the sources of variability in white matter hyperintensity (WMH) measures across two major studies of healthy elderly populations (Whitehall II imaging sub-study and UK Biobank). Harmonisation procedures were developed and tested to remove or model different sources of non-biological variability. A parser was created to harmonise non-imaging variables that are relevant for WMH across the two datasets. Processing strategies that maximise the consistency across datasets, and utilise multivariate regression to characterise sample differences contributing to study-level differences in WMH variations, were then identified.

The worked showed that by including a number of specific standardised processing steps, and appropriate modelling of sample differences, through the alignment of demographic, cognitive and physiological variables, highly calibrated WMH measures from these datasets can be provided. Finally, the impact of WMH definition and sub-classification on the relationship between WMHs and cognition was explored.

These results open up a huge range of applications for the study of WMH and other neuroimaging markers across extensive databases of clinical data.

Summary of Outputs: (as per Researchfish categories)

Publications (as April 2020):

- *Sundaresan V, Zamboni G, Le Heron C, Rothwell PM, Husain M, Battaglini M, De Stefano N, Jenkinson M,* ***Griffanti L.*** *Automated lesion segmentation with BIANCA: Impact of population-level features, classification algorithm and locally adaptive thresholding. Neuroimage. 2019;202:116056. (https://www.sciencedirect.com/science/article/pii/S105381191930638X?via%3Dihub)*

This work improved the automated quantification of white matter hyperintensities (WMHs). It allowed more accurate estimates of WMH and explored the variability in WMH measures that can be due to the tool (and its settings) used for the analyses.

In preparation:

1) "Integration of large-scale neuroimaging research datasets: harmonisation of White Matter Hyperintensity measurements across Whitehall and UK Biobank datasets"
2) "Classifying white matter hyperintensities according to intensity and spatial localisation reveals specific association with cognition."

Collaborations & Partnerships

- Collaboration with Università degli Studi di Milano, San Donato. PI: Prof. Francesco Sardanelli, Student: Dr. Luca Melazzini.
- Collaboration with Politecnico di Milano. PI: Prof. Giuseppe Baselli, Students: Valentina Bordin, Ilaria Bertani.

Further Funding

- Ludovica Griffanti applied for an Alzheimer's Society Senior Fellowship to build upon the work carried out in this project. The results obtained in this project represented an important portion of the work which led to the Fellowship proposal.

Next Destinations

- Valentina Bordin is applying for a PhD in biomedical engineering. Thanks to the skills learnt as part of this project, she is planning focus on assessing the utility of MRI as a marker for evaluating the efficacy of tele-rehabilitation in dementia and chronic neurological conditions
- Ludovica Griffanti joined the Psychiatry Department in Oxford as postdoctoral researcher. In her new role she will expand her harmonisation work to other MRI-derived measures and clinical datasets.

Engagement Activities

2019

- June 2019, poster presentation at the organisation for human brain mapping (OHBM) conference. Title: *"Harmonising measures of white matter hyperintensities across sites and studies: impact of training and manual rating in FSL-BIANCA". Griffanti et al.*
- 1st July 2019, preliminary results presented by Ludovica Griffanti at the MRI dementia conference 2019, St Anne's College, University of Oxford. Title: *"Harmonising MR analysis across sites "*
- December 2019, abstract accepted (oral presentation) at the European Congress of Radiology (ECR) 2020 [postponed to July 2020]. Title: *"Between- and within-rater agreement in white matter hyperintensitiy segmentation from manual rating and a supervised automated classifier, FSL-BIANCA". Griffanti et al.*
- December 2019, abstract accepted (oral presentation) at the European Congress of Radiology (ECR) 2020 [postponed to July 2020]. Title: *"Classifying white matter hyperintensities according to intensity and spatial localisation reveals specific association with cognition". Melazzini et al.*

Influence of policy, practice, patients & the public

- The methods and tools developed in this project can be applied to different datasets and MRI modalities. Future directions include normative modelling to compare individual measures to a normative population (UK Biobank). This in turn will allow the use of quantitative measures derived from MRI in clinical settings

Research Tools & Methods

- Configuration file for funpack (https://git.fmrib.ox.ac.uk/fsl/funpack/) to automatically obtain matched variables UKB - WHII available on DPUK git (https://issues.dpuk.org/eugeneduff/wmh_harmonisation)

Research Databases & Models

None

Intellectual property & licencing

None

Medical products, interventions & clinical trials

None

Artistic & creative products

None

Software & technical products

None

Spin outs

None

Awards & recognition

None

Other outputs & knowledge/future steps

None

Use of facilities & resources

None

Most successful outcome and what it means for future dementia research:

Through this project the dementia research field was provided with **tools and methods to perform imaging and non-imaging data harmonisation** across datasets. Removing or accounting for different sources of variability will increase statistical power, enable better, more sensitive, analyses and ultimately allow the definitions of better biomarkers.

In addition, it has **contributed substantially to Dr Griffanti's career development** allowing her to drive her own project and supervise other research staff. It allowed other researchers to get involved in dementia research. In this project two international MSc students (Valentina Bordin and Ilaria Bertani, Politecnico di Milano, Italy) and one international PhD student (Dr Luca Melazzini, Università degli studi di Milano, Italy) were able to contribute. It has also enhanced Dr Griffanti's supervision record; Dr Griffanti and her colleague, Dr Duff, successfully supervised the two MSc students to their degrees (graduation December 2019), a journal paper is in preparation, and Valentina Bordin decided to remain in the dementia research field and to apply for a PhD. The project carried out by Luca Melazzini will be part of his PhD thesis and a paper is in preparation.

Lessons learned:

- The data access was slower and more difficult than expected. The data request through DPUK data portal was well organised but cohort owners were still working on the organisation of their imaging data on the platform. A different approach for data access was adopted. The UK Biobank dataset was accessed with an ad-hoc application via the Access Management System and a collaboration put in place with the Whitehall II imaging sub-study (PI: Prof. Klaus Ebmeier). Given the delays in finalising agreements between DPUK and Lothian Birth Cohort (LBC) this cohort was not used and the harmonisation study focused on two datasets: Whitehall II (data acquired on two scanners) and UK Biobank. This still allowed the development and testing of harmonisation methods for two different scenarios: a 'multi-centre study' (Whitehall II – same population, same MRI protocol, different scanner) and a 'retrospective datasets merging' (Whitehall and UKB).
- The matching of the non-imaging variables was also more complex than expected. However, this also led to one of the most successful outcomes of the project: a detailed and generalisable matching strategy was developed and the code is now accessible and customizable to adapt to different variables and datasets.
- The proposed approach for WMH measures harmonisation was successful in removing non-biological variability from the data and make measures more comparable across datasets. It confirmed that significant improvements can be made implementing harmonisation strategies at different levels: at the pre-processing level (bias field correction), at the WMH measures extraction level (BIANCA settings) and at the analysis level (modelling non-imaging differences across datasets).

Other:

Nothing further to report

Date of Report:

24 April 2020