Crosstalk: The Impact of Cardiac Anatomy and Function on Brain Structure and Health

Experimental Medicine Project 4

Objective(s):

The aim of this work was to apply automated image analysis to heart and brain images acquired by the UK Biobank initiative. Specifically, evidence was sought for structural/functional correlates between heart and brain in a cross-section of the mature UK population with a focus on early indicators of adverse brain changes that might be coupled across the organs. A series of investigations were carried out which aimed to explore the relationship between cardiovascular risk factors (high blood pressure, abnormal cardiac function) and the brain, paying particular attention to regions that are typically associated with cognitive impairment and autonomic regulation.

More specifically the aims were:
1) Developing an image processing pipeline for selected UK Biobank imaging data on DPUK portal
2) Undertaking correlative analysis within the brain and heart of the imaged subset
3) Undertaking a Meta-analysis and systematic review of current population-based studies reporting an association between hypertension and structural brain measures associated with age-related disease
4) To develop methodology to return brain and cardiac structural processed data to UK Biobank.

Overview Summary:

The brain and the heart are two organs which have been studied more than any other, providing a profound, though still incomplete understanding of development, ageing and pathology. Imaging studies have allowed investigation of the structure and function of the brain and heart but have historically been studied in isolation. Thus, it is still unclear to what extent systemic vascular risk

influences brain health. The aim of this project was to apply automated image analysis to heart and brain images acquired by the UK Biobank Initiative. Early evidence of structural/functional correlates between the heart and brain in a cross-section of the mature UK adult population was sought, focusing on early indicators of adverse brain changes which are coupled across organs. This provided evidence that abnormalities in both cardiac and vascular (blood pressure/hypertension) function are coupled with abnormalities in brain structure and function as well as cognitive decline. The results from these analyses provide additional motivation for further research into age-related and pathological effects of cardiovascular function on the brain and vice versa.

Executive Summary:

It is widely recognised that typical cardiovascular risk factors also present greater risk of brain pathology and cognitive impairment. It is therefore of interest and importance to identify early brain correlates of cardiovascular symptoms that are associated with increased risk of neuropathology.

This project is made up of a series of investigations which explore the relationship between cardiovascular risk factors (high blood pressure, abnormal cardiac function) and the brain, paying particular attention to regions that are typically associated with cognitive impairment and autonomic regulation. Both structural and functional Magnetic Resonance Imaging (MRI) have been employed to address the aims.

A meta-analysis and systematic review of the literature was carried out to determine the relationship between (chronic) high blood pressure and grey/white matter structural indices. Brain and cardiac images from a large cohort (n = ~13000) were processed yielding useful metrics, which were then used to investigate relationships between the heart and brain.

Results showed that hypertension is associated with greater white matter hyperintensity volume and severity, localised cerebral cortical thinning and weaker functional connectivity within localised regions previously implicated in blood pressure regulation, the insula. This group is the first to show that in neurologically healthy hypertensive individuals, functional connectivity of the anterior insula, is different than in normotensive counterparts. The insula has previously been implicated in dementia.

Furthermore, individuals with abnormal cardiac function display reduced spontaneous brain activity and weaker functional connectivity in localised frontal brain areas. This reduced brain activity was related to worse performance on a test of executive function.

These results provide strong evidence that localised brain abnormalities are associated with cardiovascular dysfunction. Further work is necessary to determine the causal relationship and if these findings have clinical utility.

Summary of Outputs: (as per Researchfish categories)

Publications:

PUBLISHED:

- Worker, A., Dima, D., Combes, A., Crum, WR., Streffer, J., Einstein, S., Mehta, MA., Barker, GJ., Williams, SCR., O'Daly, O. 2018. Test-Retest Reliability and Longitudinal Analysis of Automated Hippocampal Subregion Volumes in Healthy Ageing and Alzheimer's Disease Populations. Human Brain Mapping 39 (4):1743-54. https://doi.org/10.1002/hbm.23948.

An automated hippocampal subregion segmentation pipeline was applied to longitudinally acquired T1-weighted MRI scans. Test–retest reliability and sensitivity to longitudinal change was estimated. The results show that 20/24 subregion volume estimates had ICC scores of 0.9 or higher. Longitudinal analysis demonstrated sensitivity to rate of volume change over time in several hippocampal subregions (CA1, molecular layer, CA3, hippocampal tail, fissure and presubiculum).

IN REVIEW (April 2020)

- Worker, A., O, O'Daly., Matthews, P. M., Williams, S. C., Dima, D. Anterior insula functional connectivity in hypertension. Under review.

A comparison between anterior insula resting-state functional connectivity in neurologically healthy untreated hypertension and normotension was made. Relative to the normotensive group, untreated hypertensive participants had weaker intra-insula functional connectivity and weaker inter-insula connectivity of the right dorsal dysgranular insula to the right postcentral gyrus. These results suggest that the anterior insula may be relevant to the development or progression of hypertension.

- Worker, A., Dima, D., Matthews, P. M., Williams, S. C., O'Daly, O. Altered brain functional properties associated with cognitive ability in males with abnormal cardiac function. Under Review.

This study describes the first examination of brain function and cognition in a mid-life sample of males (n=303) with abnormal left ventricular ejection fraction (LVEF). In regard to brain function, males with high LVEF compared to healthy participants displayed different function in the medial orbitofrontal cortex. Within the high LVEF group, orbitofrontal function was associated with scores of fluid intelligence.

- Worker, A., Kempton, M., Dima, D. The relationship between hypertension and white matter hyperintensities: a meta-analysis and systematic review of cross-sectional studies. Under Review.

A meta-analysis and systematic review of studies assessing the relationship between hypertension/blood pressure and brain structure was conducted. Twenty-five studies were included. The results revealed a weak but significant relationship between hypertension and white matter hyperintensity severity. The systematic review did not demonstrate an influence of hypertension on age-related changes in total brain volume or hippocampal volume.

IN PREPARATION (APRIL 2020)

- Worker, A., O, O'Daly., Matthews, P. M., Williams, S. C., Dima, D. The relationship between hypertension and cortical thickness. In preparation.

Cortical thickness measures of 10,262 healthy participants (ages 44-80) taken from the UK Biobank cohort, were derived. General linear model regression identified a negative linear relationship between systolic blood pressure and cortical thickness in temporal, anterior insula and fusiform/entorhinal cortex. Higher diastolic blood pressure was associated with thinner cortex in the insula, anterior cingulate and superior temporal gyrus

Collaborations & Partnerships

This project facilitated a collaboration between the teams of Professor Steve Williams (KCL) and Professor Paul Matthews (ICL).

Further Funding

The promising avenues arising from this work will be followed up, and form part of future grant applications.

Next Destinations

Amanda Worker's PhD thesis has been submitted and she is due to defend it in May 2020. She is currently focusing on getting the manuscripts described above published. She will continue to follow-up on new releases of UK Biobank data with the aim of continuing these analyses in this project longitudinally.

Engagement Activities

- Presentation of meta-analysis at the Organisation of Human Brain Mapping Conference in 2018
- Presentation of results from analysis of cardiac MRI and brain measures at the Organisation Human Brain Mapping Conference 2019

Influence of policy, practice, patients & the public

None

Research Tools & Methods

All analytical models have been implemented in existing software packages (e.g. Freesurfer and SPM)

Research Databases & Models

The results of this project will be made available to UK Biobank and wider community upon publication.

Intellectual property & licencing

None

Medical products, interventions & clinical trials

None

Artistic & creative products

None

Software & technical products

None

Spin outs

None

Awards & recognition

Amanda Worker's PhD thesis has been submitted and will be defended in May 2020.

Other outputs & knowledge/future steps

None

Use of facilities & resources

None
Most successful outcome and what it means for future dementia research:
This group is the first to show that in neurologically healthy hypertensive individuals, functional connectivity of the anterior insula, is different than in normotensive counterparts. Hypertension is a modifiable risk factor for dementia. The insula has previously been implicated in dementia. It is possible that the results from this study are early indicators of dementia related pathology
Lessons learned:
- The download and processing of the initial 13,000 brain structural scans went smoothly. It is clear that the time spent on setting up infrastructure contributed to this.   - There were challenges around storage and back-up of the large amount of data generated in the project. A second copy of processed data is currently held on hard-disk, with discussions in the group needed to ensure disruption to other research projects was minimised. Data storage and back-up is likely to take on greater significance as larger and larger datasets are created.   - The datasets facilitated a significant number of hypothesis-driven analyses. The work has generated a number of interesting findings that will be pursued in future projects focusing on the mechanisms involved.   - In terms of analyses, the availability of different sets of data at different times meant that several sub-projects were running in parallel. This led to several manuscripts being preparation/under review at the same time, rather than having one published before moving onto the next. On refection, it may have been more effective to focus on each sub-project but the timeline was dictated by data availability plus understanding how to acquire the measures and what they represented.
Other:
Nothing further to report
Date of Report:
27 April 2020