Banking on Brains: The UK Brain Bank Network

https://mrc.ukri.org/research/facilities-and-resources-for-researchers/brain-banks/

Abstract: Human post-mortem brain tissue remains one of the most important resources for neuroscience research and its collection and provision is essential if we are to develop new strategies and treatments for neurodegenerative and psychiatric disease. The scientific value of the tissue is greatly increased when accompanied by in depth clinical and neuropathological assessment. The MRC UK brain bank network was founded in 2013 to bring together the brain tissue resources within the UK. We are constantly updating our procedures to ensure tissue is of the best quality for use in current research techniques, striving to reduce post-mortem delay, limit pH change and maintain DNA/RNA integrity. We have collections of a wide variety of diseases, including Alzheimer's disease, Dementia with Lewy Bodies, Motor Neurone Disease and Frontotemporal dementia. However, we also collect tissue from rarer diseases, such as psychosis, head injury and paediatric disorders. In order to provide comparative control tissue we also house a strong collection of healthy brain and spinal cord tissue. All donations undergo a comprehensive histological examination to provide detailed information on disease pathology. The brain banks operate a transparent and open-door policy for provision of this tissue to researchers and all tissue is entered into a central, searchable database.

What is the UK Brain Bank Network?

The UK Brain Banks Network is an initiative, led by the MRC, to establish a coordinated national network of UK brain tissue resources for researchers to use. The banks store post-mortem brain and central nervous system (CNS) tissue donated by the public for diagnosis and research into disorders. Advances in understanding genetics and many of the molecules that define brain function mean that more and more research questions can be answered from human brain tissue.

The UK Brain Banks Network supplies tissue samples to academic and industry researchers in the UK and abroad. All brain banks in the Network have REC approval to provide tissue samples to research projects and pilot studies. Approval is based on scientific merit and takes into account ethical issues (if peer review and individual ethics approval has not yet been obtained).

The banks work together to agree common standards of operation and to harmonise protocols for consent, tissue handling and storage, quality indicators and the application process for access to tissue samples.

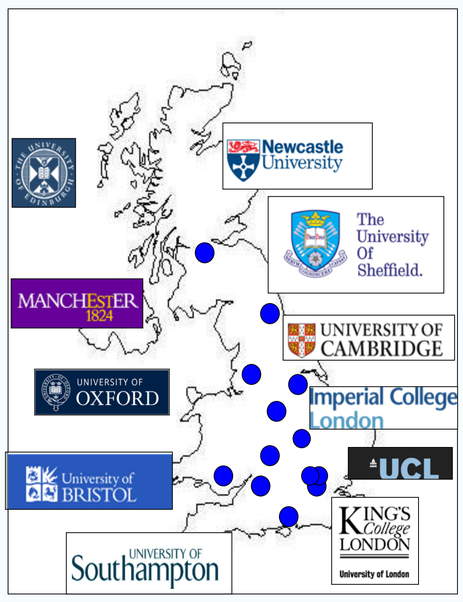
The Network, directed by Professor Seth Love, is overseen by a Steering Committee and is managed by a Network Management Group.

A central, searchable tissue database is available for registered researchers to see all available tissue *https://brainbanknetwork.cse.bris.ac.uk*

Brain banks in the Network

Brain banks in the Network are distributed across the country and donors register with the brain bank nearest to them. Researchers can apply to use tissue from any bank, some of which specialise in different disease areas, for example: dementia, multiple sclerosis, Parkinson's and autism. An important early aim of the Network was to improve the supply of 'healthy' tissue that can be used in scientific studies as a control (or comparison) for tissue samples from patients with neurological disease.

Member brain banks

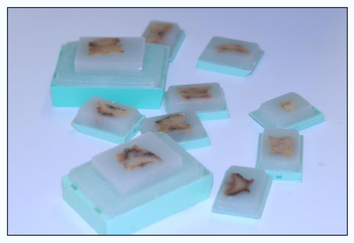


Tissue available

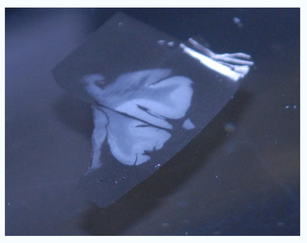
Alzheimer's disease (AD)	Huntington's Disease
AD-familial	Head injury
AD & Cerebral Vascular Disease (CVD)	Motor Neurone Disease/ALS
AD & DLB	MND/ALS – Familial
Argyrophilic grain disease	Multiple system atrophy
Ataxia	Parkinson's Disease
Autism	Pick's disease
Batten's Disease	Posterior cortical atrophy
Cerebral vascular disease	Progressive supranuclear palsy
Corticobasal degeneration	Prion disease (CJD)
Dementia with Lewy Bodies (DLB)	Rett Syndrome
Down's syndrome	Schizophrenia
Epilepsy	Tuberous sclerosis
Frontotemporal lobar degeneration	Wernicke's encephalopathy
Spinal cord (in some cases)	CSF (in some cases)

Tissue dissection and diagnosis

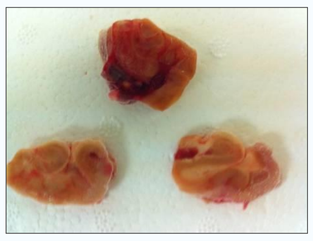
Sets of standard protocols are in use for tissue sampling of fresh and formalin fixed material. The brain is divided along the midline in the sagittal plane: one half to be fixed, while the other is freshly sliced and regions snap frozen and stored at -80°C. The formalin fixed half of the brain is examined by neuropathologists to provide diagnosis according to a comprehensive protocol which not only reaches a definitive diagnosis, but also includes details of the load and staging of pathology and other information important for researchers.



Formalin fixed paraffin embedded blocks



Formalin fixed paraffin embedded section



Frozen blocks from amygdala and hippocampus

Tissue provision

The network has a transparent and open-door policy for providing tissue to requestors from any institution without prejudice, on the condition that ethical requirements are satisfied and that a scientifically sound case underlies the application. The researchers are asked to complete a request application providing an abstract of the project, source of funding and other aspects which is assessed by the relevant bank's approval committee.

Since its initiation, the network has fulfilled over 1,000 requests; supplying over 350,000 samples. Sample provision has been acknowledged in over 500 publications.

Case study: DRI multi-omics project (Led by Prof. Paul Matthews)

Summary:

Neurodegenerative disease, and in particular Alzheimer's Disease (AD), is manifest through interactions between cells throughout the brain; it is not a cell- or region- autonomous process and the pathology evolves in a complex way from primary dysfunction through to secondary pathology. Characterising these changes is central to the development of new diagnostic, monitoring or therapeutic tools. Multi-'omics is the analysis of several different 'omes' such as the genome, proteome and transcriptome to inform on what happens at the different levels of the disease from genetic changes to how the genome is 'read' and translated into proteins.

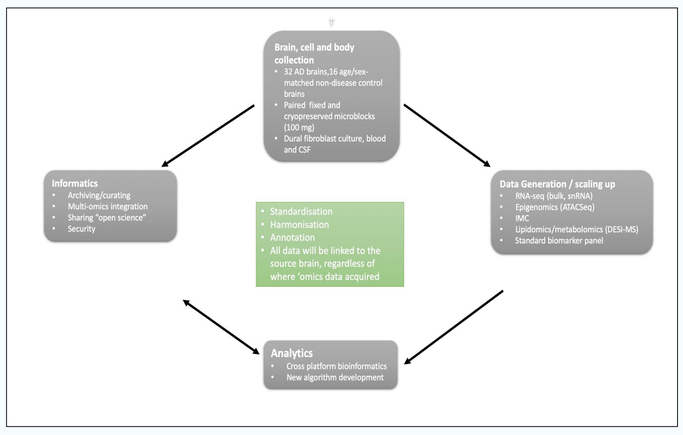
This project (MAP AD) is undertaking acquisition of well-phenotyped human brain tissue to generate multi-scale (cells, regions and whole brain) and multi-platform (genomics, proteomics, transcriptomics) across different stages of the disease. A multi-'omic characterisation of human AD brains at different stages of the disease will be run with the ability to trace all data back to The individual brain and compare and correlate it with other pathological hallmarks. Developing resources for interrogation of such multi-dimensional, big data by multiple users is key to gaining further understanding of the disease processes, developing biomarkers for use in clinical trials and, ultimately, for identifying new drug targets.

Strategy

The *scientific strategy* for MAP AD will enable development of a comprehensive, disease-based multi-omic atlas or database, focusing initially on common set of well-characterised Alzheimer's disease and matched, disease-free control brains.

Over an initial three years, this project is intended to demonstrate the potential for high impact of a multi-omics resource coordinated by the UK DRI through:

- Careful identification of brains with well-defined, well-annotated characteristics for use in this pilot project and by UK DRI and other researchers
- Archiving of multiple microblocks from at several, neuropathologically distinct regions of each brain
- Optimisation of cell culture methods for generation of induced pluripotential cells from dura associated with this brains (in partnership with the UK DRI at Cardiff)
- Demonstration of the value of linked, multi-omic characterisations of the molecular neuropathology
- Development and maintenance of openly accessible analytical pipelines to enable analyses and visualisation
- Characterisation of disease-, stage- and cell-specific molecular neuropathology for Alzheimer's disease
- External partnerships and open data sharing



Techniques/measurements

- Transcriptomics (RNASeq including small RNA, snRNASeq) (Imperial) and ATAC Seq
- Hypothesis-led spatial transcriptomic tissue characterisations (RNAScope, BaseScope)
- Untargeted spatial lipidomics with a particular focus on oxidative stress-related changes
- Targeted proteomics (IMC)

The Bristol Brain Bank will perform a standard set of biochemical assays on microblocks from each region of each of the 48 brains (after transfer of brains selected from the Edinburgh, KCL and UCL brain banks for inclusion in the AD [n=32] or non-disease control [n=16] sets). The Imperial site additionally will genotype one microblock from all brains characterised pathologically (n~100).

Tissue multi-omics characterisations will be performed at the Imperial and UCL (and potentially other) UK DRI at the level of the single cell (e.g., with snRNASeq, scATACSeq) and using multi-cellular phenotypes that preserve anatomical detail (e.g, RNAScope, BaseScope, smFISH, MERFISH, imaging mass cytometry and DESI-MS for lipidomics). Pilot work to link this to synaptic proteome characterisation is intended to be developed over the course of the pilot within the Edinburgh UK DRI.

The availability of multiple micro-blocks from the same regions of the same brains will facilitate sharing of the tissue resource to enable future integration of new data from additional 'omics methods by other UK DRI and external investigators.

Value:

This project relies on the ability of the UK Brain bank network to process new tissue donations in a responsive manner to meet the needs of cutting-edge neuroscience research. Sampling has been standardised across the banks involved and the neuropathological assessment of the tissue will play a major role in the analysis of the results as the work progresses.

We Thank the donors and their families for the gift of tissue. Funding for the banks in the network is provided by the MRC, Alzheimer's Society, ARUK, Autistica, BRACE, Multiple Sclerosis Society and Parkinson's UK